Wiadomości Lekarskie

Czasopismo Polskiego Towarzystwa Lekarskiego

Pamięci
dra Władysława
Biegańskiego

TOM LXXII, 2019, Nr 7, lipiec

Rok założenia 1928

Aluna Publishing

Wiadomości Lekarskie is abstracted and indexed in: PubMed/Medline, EBSCO, SCOPUS, Index Copernicus, Polish Medical Library (GBL), Polish Ministry of Science and Higher Education.

Zasady prenumeraty miesięcznika Wiadomości Lekarskie na rok 2019

Zamówienia na prenumeratę przyjmuje Wydawnictwo Aluna:

– e-mailem: prenumerata@wydawnictwo-aluna.pl
– listownie na adres:

Wydawnictwo Aluna
ul. Z.M. Przesmyckiego 29, 05-510 Konstancin-Jeziorna

Prosimy o dokonywanie wpłat na numer rachunku Wydawnictwa:
Credit Agricole Bank Polska S. A.: 82 1940 1076 3010 7407 0000 0000

Cena prenumeraty dwunastu kolejnych numerów: 240 zł/rok (w tym 5% VAT)

Cena prenumeraty zagranicznej: 120 euro/rok.
Cena pojedynczego numeru – 30 zł (w tym 5% VAT) + koszt przesyłki.
Przed dokonaniem wpłaty prosimy o złożenie zamówienia.

Wiadomości Lekarskie

Managing Editor:
Agnieszka Rosa amarosa@wp.pl

International Editor:
Lesia Rudenko l.rudenko@wydawnictwo-aluna.pl

Distribution and Subscriptions:
Bartosz Guterman prenumerata@wydawnictwo-aluna.pl

Graphic design / production:
Grzegorz Sztank www.red-studio.eu

Publisher:
ALUNA Publishing
ul. Przesmyckiego 29, 05-510 Konstancin – Jeziorna
www.aluna.waw.pl www.wiadomoscilekarskie.pl
www.medlist.org

REGULAMIN PRZYJMOWANIA I OGŁASZANIA PRAC W WIADOMOŚCIACH LEKARSKICH

1. Miesięcznik Wiadomości Lekarskie jest czasopismem Polskiego Towarzystwa Lekarskiego, ma charakter naukowo-edukacyjny. Zamieszczane są w nim prace oryginalne, kliniczne i doświadczalne oraz poglądowe w języku polskim lub angielskim oraz innych językach (za zgodą redakcji).
2. Publikacja pracy w Wiadomościach Lekarskich jest płatna. Od stycznia 2017 roku koszt opublikowania artykułu wynosi 1000 zł plus 23%VAT. Jeżeli pierwszym autorem pracy jest członek Rady Naukowej czasopisma lub zespołu recenzentów – za druk nie pracy nie pobieramy opłaty, jeśli zaś jest kolejnym współautorem – opłata wynosi 500 zł plus 23%VAT. Wydawca wystawia faktury. Opłatę należy uiścić po otrzymaniu pozytywnej recenzji, przed opublikowaniem pracy. Z opłaty za publikację zwolnieni są członkowie Polskiego Towarzystwa Lekarskiego z udokumentowaną opłatą za składki członkowskie za ostatnie 3 lata.
3. Prace zapisane w formacie DOC (z wyłączeniem rycin, które powinny stanowić osobne pliki) należy przesłać pocztą elektroniczną na adres redakcji: Agnieszka Rosa - amarosa@wp.pl.
4. Objętość prac oryginalnych – łącznie z rycinami i piśmiennictwem – nie może przekraczać 21 600 znaków (12 stron maszynopisu), prac poglądowych – do 36 000 znaków (20 stron).
5. Strona tytułowa powinna zawierać:
   – tytuł w języku angielskim i polskim,
   – pełne imiona i nazwiska autorów,
   – afiliację autorów,
6. Praca oryginalna powinna mieć następującą strukturę: wstęp, cel pracy, materiał i metody, wyniki, dyskusja i wnioski, które nie mogą być streszczeniem pracy. Przy zastosowaniu skrótów konieczne jest podanie pełnego brzmienia terminu przy pierwszym użyciu. W pracach doświadczalnych, w których wykonano badania na ludziach lub zwierzętach, a także w badaniach klinicznych, należy umieścić informację o uzyskaniu zgody komisji etyki badań naukowych.
7. Streszczenia zarówno w języku polskim, jak i angielskim powinny zawierać 200-250 słów. Streszczenia prac oryginalnych, klinicznych i doświadczalnych powinny posiadać następującą strukturę: cel, materiał i metody, wyniki wnioski. Nie należy używać skrótów w tytule ani w streszczeniu.
8. Słowa kluczowe (3-6) należy podawać w języku angielskim i polskim, zgodnie z katalogami MeSH (Medical Subject Headings Index Medicus http://www.nim.nih.gov.mesh/MBrower.html). Słowa kluczowe nie mogą być powtórzeniem tytułu pracy.
9. Materiał ilustracyjny - ryciny, wykresy, rysunki, fotografie, slajdy - powinien być opisany cyframi arabskimi i zapisany jako pliki JPG, TIFF lub EPS o rozdzielczości 300 DPI (nie w plikach tekstowych). Ich opisy należy przesłać w osobnym pliku. W tekście muszą znajdować się odniesienia do wszystkich rycin (w nawisach okrągłych).
10. Tabele – ich tytuły (nad tabelą) i treść - powinny być zapisane w programie Microsoft Word, ponumerowane cyframi rzymskimi. Wszystkie stopki dotyczące tabeli powinny znajdować się poniżej tekstu tabeli. W tekście pracy należy umieścić odniesienia do wszystkich tabel (w nawiasach okrągłych).
11. W wykazie piśmiennictwa ułożonym według kolejności cytowania należy uwzględnić wyłącznie te prace, na które autor powołuje się w tekście. W pracach oryginalnych nie powinno być więcej niż 30 pozycji, a w poglądowych nie więcej niż 40 pozycji. Każda pozycja powinna zawierać: nazwiska wszystkich autorów, pierwsze litery imion, tytuł pracy, skrót tytułu czasopisma (wg Index Medicus), rok, numer, stronę początkową i końcową. Przy pozycjach książkowych należy podać: nazwisko autora (autorów), pierwszą literę imienia, tytuł rozdziału, tytuł książki, wydawnictwo, miejsce i rok wydania. Dopuszcza się cytowanie stron internetowych z podaniem adresu URL i daty użycia artykułu oraz o ile to możliwe nazwisk autorów. Każda pozycja piśmiennictwa powinna mieć odwołanie w tekście pracy umieszczone w nawiasie kwadratowym, np. [1], [3—6]. Pozycje zapisuje się w sposób zaprezentowany w Załączniku nr 1 do niniejszego regulaminu.
12. Po piśmiennictwie należy podać adres do korespondencji, nazwisko i imię pierwszego autora, adres, numer telefonu oraz adres e-mail.
13. Do pracy należy dołączyć oświadczenie podpisane przez wszystkich autorów określające udział poszczególnych autorów w przygotowaniu pracy (np. koncepcja i projekt pracy, zbieranie danych i ich analiza, odpowiedzialność za analizę statystyczną, napisanie artykułu, krytyczna recenzja itd.), a także oświadczenie, że biorą oni odpowiedzialność za treść. Ponadto należy zaznaczyć, że praca nie była publikowana ani zgłaszana do druku w innym czasopiśmie.
14. Jednocześnie autorzy powinni podać do wiadomości wszelkie inne informacje mogące wskazywać na istnienie konfliktu interesów, takie jak:
   – zależności finansowe (zatrudnienie, płatna ekspertyza, doradztwo, posiadanie akcji, honoraria),
   – zależności osobiste,
   – współzawodnictwo akademickie i inne mogące mieć wpływ na stronę merytoryczną pracy,
   – sponsorowanie całości lub części badań na etapie projektowania, zbierania, analizy i interpretacji danych lub pisanie raportu.

   Konflikt interesów ma miejsce wtedy, gdy przynajmniej jeden z autorów ma powiązania lub zależności finansowe z przemysłem bezpośrednie lub za pośrednictwem najbliższej rodziny. Jeśli praca dotyczy badań nad produktami częściowo lub całkowicie sponsorowanymi przez firmy, autorzy mają obowiązek ujawnić ten fakt w załączonym oświadczeniu.
15. Każda praca podlega weryfikacji w systemie antyplagiatowym (zapora ghostwriting).
16. Redakcja przestrzega zasad zawartych w Deklaracji Helsińskiej, a także w Interdisciplinary and Guidlines for the Use of Animals In Research, Testing and Education, wydanych przez New York Academy nof Sciencees' Adhoc Resarch. Wszystkie prace odnoszące się do zwierząt lub ludzi muszą być zgodne z zasadami etyki określanymi przez Komisję Etyczną.
17. Czasopismo recenzowane jest w trybie podwójnej, ślepej recenzji. Nadesłane prace są oceniane przez dwóch niezależnych recenzentów, a następnie kwalifikowane do druku przez Redaktora Naczelnego. Recenzje mają charakter anonimowy. Krytyczne recenzje autorzy otrzymują wraz z prośbą o poprawienie pracy lub z decyzją o niezakwalifikowaniu jej do druku. Procedura recenzowania artykułów jest zgodna z zaleceniami Ministerstwa Nauki i Szkolnictwa Wyższego zawartymi w opracowaniu „Dobre praktyki w procedurach recenzyjnych w nauce" (Warszawa 2011) i szczegółowo została opisana na stronie http://www.nauka.gov.pl/g2/oryginal/2014_02/307f933b1a75d6705a4406d5452d6dbf.pdf
18. Redakcja zastrzega sobie prawo redagowania nadesłanych tekstów (dokonywania skrótów i poprawek). Prace są wysyłane do akceptacji autorów. Poprawki autorskie należy przesłać w terminie 3 dni od daty wysłania wiadomości e-mail (pocztą elektroniczną). Brak odpowiedzi w podanym terminie jest równoznaczny z akceptacją przez autora nadesłanego materiału.
19. Przyjęcie pracy do druku oznacza przejęcie praw autorskich przez Redakcję Wiadomości Lekarskich.
20. Autorzy otrzymują nieodpłatnie plik PDF wydania, w którym znajduje się ich praca, a na życzenie - egzemplarz drukowany. Plik elektroniczny przeznaczony jest do indywidualnego użytku autora, bez prawa do rozpowszechniania bez zgody redakcji.
21. Prace przygotowane niezgodnie z regulaminem zostaną zwrócone autorom do poprawienia.
22. Redakcja nie odpowiada za treść zamieszczanych reklam.

CONTENS / SPIS TREŚCI

REVIEW ARTICLES / PRACE POGLĄDOWE

CASE REPORTS /OPISY PRZYPADKÓW

ARTYKUŁ REDAKCYJNY
EDITORIAL ARTICLE

MODERN METHODS OF TREATMENT IN PALLIATIVE CARE

NOWOCZESNE METODY LECZENIA W OPIECE PALIATYWNEJ

Ewa Kucharska[1], Aleksandra Kucharska[2], Aleksander Sieroń[3], Mariusz Nowakowski[4], Karolina Sieroń[5]
[1]DEPARTMENT OF GERONTOLOGY, GERIATRICS AND SOCIAL WORK JESUIT UNIVERSITY IGNATIANUM IN KRAKÓW, KRAKOW, POLAND
[2]JAGIELLONIAN UNIVERSITY MEDICAL COLLEGE IN KRAKÓW, KRAKOW, POLAND
[3]DEPARTMENT OF PHYSIOTHERAPY, JAN DLUGOSZ UNIVERSITY IN CZESTOCHOWA, CZESTOCHOWA, POLAND
[4]VADIMED MEDICAL CENTER IN KRAKÓW, KRAKOW, POLAND
[5]SCHOOL OF HEALTH SCIENCES IN KATOWICE, CHAIR OF PHYSIOTHERAPY, DEPARTMENT OF PHYSICAL MEDICINE, MEDICAL UNIVERSITY OF SILESIA IN KATOWICE, KATOWICE, POLAND

ABSTRACT

The palliative care patient is definitely a unique type of patient. Due to the complexity of the symptoms requires a holistic therapeutic approach. Modern methods of treatment in palliative and hospice care underline an important role of physio, kinesiotherapy and pharmacological treatment coexistence. The rehabilitation reduces clinical symptoms, accompanying the basic disease and increases the quality of life of palliative patients and their families. It becomes an inseparable element of treatment, both in outpatient care as well as in stationary care and home care. Due to the high dynamics onset of cancer in the group of geriatric patients there is a need for a broader analysis of the topic. The goal of palliative care is to achieve the best possible quality of life for patients and their families.

KEY WORDS: geriatrics, palliative and hospice care, physiotherapy, kinesiotherapy

STRESZCZENIE

Pacjent w opiece paliatywnej jest zdecydowanie wyjątkowym typem pacjenta. Ze względu na złożoność objawów wymaga holistycznego podejścia terapeutycznego. Współczesne metody leczenia w opiece paliatywnej i hospicyjnej podkreślają ważną rolę współistnienia fizjoterapii, kinezyterapii i leczenia farmakologicznego. Rehabilitacja zmniejsza objawy kliniczne towarzyszące chorobie podstawowej i podnosi jakość życia pacjentów paliatywnych i ich rodzin. Staje się nieodłącznym elementem leczenia zarówno w opiece ambulatoryjnej, jak i w opiece stacjonarnej i domowej. Ze względu na wysoką dynamikę zachorowań na raka w grupie pacjentów geriatrycznych istnieje potrzeba szerszej analizy tematu. Celem opieki paliatywnej jest osiągnięcie jak najlepszej jakości życia pacjentów i ich rodzin.

SŁOWA KLUCZOWE: geriatria, opieka paliatywna i hospicyjna, fizjoterapia, kinezyterapia

Wiad Lek 2019, 72, 7, 1229-1235

INTRODUCTION

The world of marketing and advertising, Internet and the latest media technology favours the understanding of suffering and hospice care as an exceptionally negative period. In such a perspective, efforts should be made to trigger sensitivity to suffering in young people, in particular the suffering of a person requiring hospice and palliative care, understood in the holistic dimension.

Physical therapy, also known as physiotherapy is an integral part of the basic therapy. Acording to the definition it is one of the allied health professions that, by using mechanical force and movements (bio-mechanics or kinesiology), manual therapy, exercise therapy, and electrotherapy, remediates impairments and promotes mobility and function.It has also found a significant place among the treatment methods used in the group of elderly and terminally ill people, due to the progressing medicalization and saving human life to the end, as well as the tendency to significantly reduce the symptoms associated with the basic disease. It influences the alleviation of clinical ailments and improvement of quality of life in case of palliative patients.

DYSPNOEA

Very serious symptom in the course of cancer is dyspnoea. This breathlessness may result from the very essence of cancer, as well as from the accompanying pathology of the respiratory system. Cancer dyspnoea is a symptom of lung cancer, which can occur on its own or in the course of other diseases. Dyspnoea is defined as a subjectively noticeable difficulty in breathing. It is a very individual feeling, which depends on many factors, among others: the mechanism of dyspnoea development, mental and physical condition of the patient, and his family and social

situation. 70% of oncological patients in the last weeks of life suffer from this symptom [1]. The most common cancers that cause dyspnoea directly include: lung cancer, colorectal cancer, breast cancer and prostate cancer. The aetiology of dyspnoea in oncological patients varies, but in lung cancer patients dyspnoea is the result of closure of large airways or significant reduction of gas exchange surfaces by infiltration of large parts of the pulmonary parenchyma or by compression from the outside in the course of exudate to the pleura. In patients with lung cancer the feeling of dyspnoea occurs in 60-70% of patients. Depending on the type of cause, different forms of causal treatment of dyspnoea are used, e.g. brachytherapy or drainage of the pleural cavity. In case of narrowing or closure of the upper respiratory tract or bronchi, palliative radiotherapy is used, and in rare cases chemotherapy with cytostatic drugs. The use of drugs reducing dyspnoea is a supportive treatment, the first-line drug may be morphine, which acts in a way that reduces the symptoms of dyspnoea and has an analgesic effect. It is worth remembering that non-pharmacological procedures reducing symptoms of dyspnoea, physical therapy, relaxation techniques and increased air humidity play an important role, and in case of indications - oxygen therapy, which can bring relief from dyspnoea. In respiratory therapy, active exercises of respiratory muscles, techniques of respiratory relaxation, learning the correct respiratory tract, as well as learning effective cough are used. [2] In case of patients with lung cancer, exercises according to the POCHP concept often play an important role together with the accompanying PNF [3]. The development of an appropriate respiratory mechanism results in increased chest activity during breathing, increased chest expansion, reduced stagnant capacity and the possibility of better expectoration. Activation of the smaller thoracic muscle or the Sternocleidomastoid increases muscle elasticity, improves cage motion mechanics and increases inspiratory volume [4]. In advanced cancer, weakened respiratory muscles cause secretion build-up and impediment to breathing. In case of patients undergoing chemotherapy or radiotherapy, neuromobilisation or visceral techniques are necessary. In case of bedridden patients, breathing exercises, mobilisation of ribs, diaphragms and shoulder blades are particularly important. In case of oncological patients, increased dyspnoea is often associated with fear of death due to an increased lack of air. Therefore, proper preparation of the patient through the development of specific positions to facilitate breathing, as well as proper breathing exercises and education of the patient in the field of proceeding is extremely important [5]. Physiotherapy in palliative care of patients with respiratory disorders is carried out in hospitals as well as at home, due to respiratory insufficiency and secretion retention, respiratory tract cleaning techniques are very important. As the American Thoracic Society emphasizes, this form of proceeding is extremely important in lung diseases. Pulmonary rehabilitation is a multidisciplinary care program for patients with chronic respiratory disorders that is individually tailored and designed to optimize physical and social performance and autonomy [6]. The ATS mentions four basic elements of pulmonary rehabilitation: [7]

1. Strength training (upper limb endurance training, low limb endurance training, strength training and respiratory muscle training),
2. Education (breathing strategies, energy saving and job simplification, end-of-life training),
3. Psychosocial behavioural intervention (stress management strategies, stress management)
4. Evaluation of the result.

It has also been noted by Lanken and colleagues that respiratory rehabilitation includes physical training, psychosocial support, nutritional therapy and self-education, including breathing strategy, use of additional oxygen, pharmacological therapy (to alleviate airway obstruction) and panic control. [8] L. Nici and colleagues state that American Thoracic Society and the European Respiratory Society have confirmed exercise training as a comprehensive component of pulmonary rehabilitation to achieve effective control of dyspnoea [9].

LYMPHOEDEMA

Lymphoedema is a very important problem in cancer patients. The aim of the therapeutic methods used is to improve the quality of life [10]. It may occur as a complication of anticancer treatment or as a result of disease progression. Lymphatic oedema occurs when a protein rich fluid is drained from the intercellular space through the lymphatic system in too small amount in relation to the amount produced. Lymphatic capillaries are present in the intercellular spaces, responsible for the filtration of part of the blood plasma and the formation of intercellular fluid. 90% of this fluid returns to circulation through capillary veins, while 10% is absorbed into capillary lymphatic vessels becoming lymphatic. Among the components of the intercellular fluid, proteins penetrate into the lymphatic vessels and return to the circulation through the lymphatic system. Lymphatic vessels transport the lymph to large venous vessels. Lymphatic vessels, such as the chest and lymphatic duct, collect lymph from the whole body, connect with each other and form two large lymphatic vessels. As a result of damage or closure of individual structures forming the lymphatic system, the removal of the intercellular fluid is impaired, which results in the accumulation of fluid and proteins that are not discharged to the lymphatic vessels. There is primary and secondary lymphoedema. The first one is associated with congenital anatomical defects of this lymphatic system. It is not related to cancer. Secondary lymphoma occurs in case of patients with cancer as a result of lymphatic damage after surgery, radiotherapy or as a result of the development of cancer. Lymphoedema most often concerns patients with malignant breast cancer, cancer of the urinary tract, prostate cancer, melanoma, lymphoma, as well as gynecological cancers such as cancer of the vulvar lips or ovary. Lymphatic oedema concerns especially women after mastectomy, and occurs in 20% of

women with mastectomy with removal of axillary lymph nodes [11]. Lower limb oedema is usually associated with urinary tract cancer, prostate cancer, melanoma, lymphoma and gynecological cancers. It may occur shortly after lymph node removal surgery or after a longer period of time after the end of the therapy. Its occurrence may be affected by the number of removed lymph nodes during surgery, e.g. removal of ten or more lymph nodes during mastectomy increases the probability of oedema in relation to people in whom only one guard node has been removed. Other factors influencing the above process include radiation therapy in the armpit, groin, pelvis, supraclavicular fossa, which leads to radiation fibrosis of tissues and loss of elasticity of lymphatic vessels. Lymphoedema is three times more common in overweight people with BMI of 30 or more. In addition, a tumor located in the pelvis or abdominal cavity may cause compression of the lymphatic vessels of the thoracic duct and increase of oedema. Lymphoedema significantly reduces the functioning of patients and their quality of life. Its location, especially in the upper or lower limb, makes it difficult to perform basic activities that are important for the patient. Increased volume of the limb and increasing disability often cause a decrease in self-esteem, cause depression, and even lead to social and professional isolation of the patient. Bacterial infections that often accompany lymphoedema cause recurrent inflammatory states and lymphoedema of the skin and subcutaneous tissue. If untreated, this condition may lead to the development of lymphatic hemangioma or epidermal cancer. Lymphoedema is the main indication for physical therapy [12]. In the course of oncological treatment, advanced renal failure, anaemia, corticoids and NLPZs exacerbate the oedema. According to the guidelines of the International Society for Lymphology, physiotherapy is the basic method of treating the lymphoedema. Comprehensive drainage therapy is used, including lymphatic drainage, multi-layer bandaging, exercises to improve lymphatic drainage and skin care [13].

Comprehensive lymphoedema therapy includes manual lymphatic drainage, drainage therapy, compression therapy (multi-layer bandage), movement therapy with breathing exercises, skin care and protection. Supplementary physiotherapy includes pneumatic compression therapy, aquavibron massage and kinesiotaping. Kinesiotaping is a method of wrapping a selected area of the body with a special patch, which is a source of mechanical stimuli. It reduces pain, reduces swelling and relaxes muscle tension. Another method of improving blood circulation is a therapeutic massage, the aim of which is to improve blood and lymph circulation and speed up the treatment of inflammatory conditions. It has a very positive effect on spine and joint pains. Acupuncture, consisting in puncturing biologically active zones of the body, has a positive effect on the functioning of internal organs. The McKenzie method is also used to treat swelling, including exercises to reduce pain of an overload, functional or structural disorders. In addition, the PNF method is applied, based on the reconstruction of lost function in the process of learning movement, muscle control and motor coordination. Another method is manual therapy, based on compression and manipulation, aimed at restoring proper positioning of discs and intervertebral structures in the spine. [14] Post-isometric muscle relaxation is aimed at relaxing muscles that are in a state of contraction, as well as eliminating pain points. In order to qualify for treatment in patients with cancer, an individual assessment of the patient should be made, depending on the patient's condition and physical fitness. CDT modification is also used, giving up the lymphatic drainage [15]. In the above-mentioned methods of treatment, oedema therapy through multilayer bandaging is extremely important. The first layer is a sleeve/backet with a protective function. The hand or foot should be pressed together by bandaging each finger separately, then a second layer of dressing, sometimes a soft bandage with a protective layer. There are different materials for bandaging, either a polyurethane sponge or a combination of different materials to adapt to the surface of the body. The third layer of the dressing in patients with lymphoedema consists of low stretch bandages applied in a spiral, eight-way with a tortoise-turtle girth around the joints, with the principle of pressure gradation. Low stretch bandages provide low rest pressure, so they can also be used at night [16]. [The method of compression therapy depends on the physical condition of the patient, as well as his or her physical and mental capacity. Today, knee- socks, stockings or compression sleeves are used as materials for compression therapy. In an advanced disease process, simultaneous pharmacotherapy is used, especially medicines that improve lymph and blood flow. In the application of complex physiotherapy of lymphatic oedema, it should be kept in mind that lymphatic drainage should be performed through circular, rotational, pumping and drawing movements [17]. It is worth emphasizing that drainage should be used starting from areas not engulfed in oedema and then proceeding to drainage of the oedematous part. There are many discussions on the use of simultaneous lymphatic drainage and compression therapy. Some part of physiotherapists are of the opinion that they can be used as two separate treatments, while others believe that they should be applied in sequence, first lymphatic drainage and then compression therapy. The use of musculoskeletal techniques stretching the skin, subcutaneous connective tissue and deep fascia also facilitates proper movement of the fascia [18]. The role of kinesiotaping in lymphoedema is also discussed. This discussion is still open. There are reports about the possibility of replacing bandaging with kinesiotaping, especially in patients intolerant to pressure. Kinesiotaping relaxes the skin, improves tissue mobility, increases lymph outflow and thus reduces pain and improves quality of life. Absolute and relative contraindications should be taken into account when qualifying patients with cancer for kinesis- and physiotherapy procedures. Absolute contraindications are: deep vein thrombosis, subcutaneous tissue inflammation, increased readiness for pulmonary embolism, past pulmonary or peripheral embolism. Relative contraindications are: advanced NYHA third and fourth degree circulatory insufficiency, peripheral

circulatory disorders, advanced peripheral atherosclerosis, unstable ischemic heart disease and diabetes [19]. When educating a patient with lymphoedema, it is important to remember to explain in detail how compression therapy is used, as well as the psychological support of the person concerned. Massage is sometimes used in lymphoedema by means of a pneumatic massage device, consisting of a multi-chamber sleeve producing variable pressure [20]. It should be noted that the lymph flow is supported by active exercises used in conjunction with breathing exercises, mobilising the function of the muscle pump and simultaneously creating a negative pressure in the chest. Resistance and isometric exercises are not performed. The main priority in the treatment of lymphoedema is to improve the patient's quality of life. Lymphoedema may also appear in the lower extremities in patients who have not been diagnosed for a long time with a progressive cancer process on the part of genitourinary organs, i.e. it is a cancer mask [21]. [A serious problem is the coexistence of lymphoedema in patients with coexisting lymphatic flow disorders and simultaneous rheumatoid disease. Lymphatic dysfunction in patients with RA in itself hinders normal lymphatic flow and thus intensifies the already existing disorders of lymphatic flow.

CONSTIPATION AND DIARRHEA

Constipation and diarrhea are very important problems in case of cancer patients. They may be the result of a primary disease, or may result from the use of chemotherapy or radiotherapy. Fecal constipation in cancer patients may also be a result of medication affecting gastrointestinal peristalsis [22]. The occurrence of recurrent diarrhoea or constipation adversely affects the course of treatment, as well as the quality of patients' life. Diarrhoea is much more common in patients shortly after radiotherapy and chemotherapy. They cause dyselectrolytemia with progressive weakness and cachexia in people, in whom the cancer process causes adverse effects. Diarrhoea may also result from coexisting inflammation of the intestinal mucosa. Apart from diarrhoea and constipation in patients with advanced cancer, 40-70% of patients complain about nausea and vomiting in the course of this disease. Nausea is an unpleasant subjective feeling, often coexisting with symptoms of the autonomic nervous system. Pale skin layers, cold sweat, salivation and tachycardia often accompany them. Vomiting is the rapid ejection of gastric contents through the mouth or nose, with a large volume of food. Vomiting is a complex process of reactions that involves coordinated action of the gastrointestinal tract, diaphragm and abdominal muscles. Nausea and vomiting can also be complications of the therapy used. Treatment of these symptoms can be divided into two groups. The first group is pharmacological treatment; the second group is non-pharmacological treatment. In non-pharmacological treatment the role of physiotherapy is observed, it is used to modify the risk factors of constipation, significantly reduces musculoskeletal imbalance and increases intestinal peristalsis [23]. An oncological patient staying in bed for a long time is threatened by habitual constipation due to lack of movement and thus impaired intestinal peristalsis. Within the treatment of these disorders we use musculoskeletal, relaxing and kinesiotaping techniques, classical massage of abdominal shells with stroking, rubbing and kneading. Improvement techniques such as: respiratory therapy, working with ribs, diaphragm and release of the upper chest opening. All this allows for quick uprightening of the patient. When recommending this method, the patient should be examined very carefully, bearing in mind the existence of contraindications such as gastrointestinal obstruction, inflammatory processes in the abdominal cavity, physical therapy in less than 6 weeks after abdominal irradiation, as well as abdominal pain of unknown aetiology [24].

FATIGUE ASSEMBLY

Cancer-related fatigue (CRF), according to M. P. Davis and colleagues, is a symptom or syndrome that affects the majority of cancer patients. Davis and colleagues claim that more than 30% of cured people report symptoms of fatigue and more than 90% of cancer patients at an advanced stage of the disease have symptoms of fatigue [25]. It should be assumed that this process is related to the course of the basic disease, it is not related to fatigue alone, as it should be assumed. Factors exacerbating the occurrence of fatigue syndrome are also side effects occurring during the treatment of cancer. The problem of the feeling of continuous fatigue, as well as the subjective feeling of insufficiency accompanying the disease, definitely negatively affects the quality of patient's life. Considering the nomenclature of the disease, fatigue syndrome according to the ICD classification is not a single symptom, but their syndrome. CRF criteria according to this classification include significant fatigue, reduced energy or increased demand for rest and at least 5 accompanying symptoms. These symptoms are: general weakness, heavy limbs, weakened concentration, decreased motivation, sleep disorders, lack of regeneration after a night's rest, the need to constantly overcome fatigue, emotional reactivity to the feeling of being tired, limitations in daily activity caused by fatigue, short term memory disorders, prolonged exhaustion after workout. These criteria are met if they occur daily or almost daily for 2 weeks during the last month. Evidence that fatigue syndrome is associated with cancer or on-going treatment and the symptoms are not a consequence of pre-existing mental disorders is also necessary to diagnose CRF. There is a discrepancy between the feeling of fatigue reported by the patients themselves and the opinion of oncologists. According to N. J. Vogelzang and colleagues [26] and S. Neveli and colleagues [27] it is clearly visible that in case of patients, the fatigue syndrome is the main symptom affecting their quality of life, while oncologists believe that pain is by far the main factor negatively affecting their life quality. Many patients do not raise the problem of fatigue during medical appointments. G. A. Curt and colleagues claim that young

people, i.e. under 65 years of age, are more likely to talk about it. [28]. Older people raise the problem of fatigue in a small percentage. In many publications it can be seen that oncologists themselves do not raise this problem. Oncologists recommend different ways of opposing fatigue, such as appropriate diet, vitamins, mood-enhancing drugs, and they do not attach importance to exercise. Fatigue syndrome in cancer can have physical and mental aspects. In the physical aspect, according to Fatigue Coalition studies, patients complain about a decrease in effort tolerance, a feeling of fatigue, often accompanied by nausea, vomiting as a consequence of treatment. It should also be noted that there are significant changes in the mental aspect, i.e. concentration and memory disorders. Patients with CRF are often marginalized by themselves, unwilling to participate in social life, do not maintain mutual relations, and often isolate themselves in professional life. According to reports, in patients who were assessed for quality of life on the basis of the HRQL survey, it can be observed that all aspects that were reflected in the survey are impaired in the course of fatigue syndrome [29]. The proceeding in case of fatigue syndrome can be divided into pharmacological and non-pharmacological proceeding. In pharmacological treatment, it is required to remember about the treatment of coexisting diseases, such as: anaemia, circulatory insufficiency, coexisting metabolic and electrolyte disorders, coexisting hypothyroidism, as well as any accompanying infections. In the course of this process, in addition to pharmacological treatment, non-pharmacological treatment is an option. Above all, physiotherapy should be taken into account in this treatment. R. K. Portenoy created an algorithm of management for patients complaining about fatigue in the course of cancer. In non-pharmacological treatment, the "6E" rule is important: education, energy conservation, exercise, energyrestoration, easingstress, eatingwell [30]. It is believed that explaining to the patient and broadly understood education will allow for good communication with the patient, which is a basic factor in the applied therapy. Side effects occurring during cancer treatment often become the main cause of fatigue syndrome. It can be stated that a high-protein diet, ensuring proper albumin levels, has a positive effect on fatigue syndrome, while deficiency, increase in inflammatory parameters, vitamin deficiency and electrolyte disorders intensify these symptoms. It should be emphasized that mental, emotional and social support also plays a very important role in the reduction of fatigue symptoms. The role of interdisciplinary palliative-hospice care teams, both for in-patient and home patients, appears here. Patients with cancer are exposed to constant stress, which adversely affects their mental well-being, as well as aggravates symptoms of anxiety, uncertainty and depression. Patient support in various aspects is extremely important. It is important to emphasize the important role of family and caregivers, who are able to reduce these symptoms through good contact with the patient. Non-pharmacological method of combating fatigue in the course of cancer is motor activation. According to the guidelines of the National Comprehensive Cancer Network (NCCN) concerning the management of CRF, a recommendation has been added to start motor activation at the moment of diagnosis [31]. In the fatigue syndrome in cancer patients, in addition to the physiotherapy used, the administration of pharmacological drugs such as glucocorticoids, erythropoietin, antidepressants or progestagens, which eliminate many other adverse physical symptoms that cause the patient's reluctance to physical activity, should not be forgotten.

SWALLOWING DISORDERS

Another syndrome that adversely affects the regenerative process in the course of cancer is dysphagia. This is a problem related to the difficulty of swallowing food in a patient with gastrointestinal cancer. It may result from damage to the upper part of the gastrointestinal tract, but also from consequences after radiotherapy and chemotherapy, causing functional disorders of the nervous and muscular systems [32]. Swallowing disorders may also result from oral mucositis, pharyngitis and oesophagitis, as well as surgical procedures, which leads to the process of fibrosis and gastrointestinal stenosis. Developing the patient's exercise program to facilitate the evacuation of food from the mouth and the appropriate swallowing process protects patients from the occurrence of aspiration pneumonia. Manual musculoskeletal techniques in the head and chest have a positive effect on maintaining proper muscle tension in the head and neck muscles, and also facilitate proper passage of food. Similarly, breathing exercises affecting the diaphragm muscle, activating the muscles of the cross section of the lumbar and thoracic spine are extremely important for patients who have been hospitalized for a long time and are unable to move [33].

SUMMARY

On the basis of observations it can be seen that in case of oncological patients the subject of motor activation is practically neglected. When recommending motor activation, it should be kept in mind to choose individual exercises taking into account accompanying diseases: cardiological, neurological, haematological. Apart from indications for rehabilitation used in palliative and hospice care, the criteria for exclusion of patients have been distinguished. L. Adamsen and colleagues [34] and F. Dimeo and colleagues [35] defined exclusion criteria for kinesitherapy procedures. These include: diastolic pressure below 45 mmHg and above 95 mmHg, heart rate above 100/min, temperature above 38 degrees, respiratory rate above 20/min, infection requiring antibiotic therapy, active bleeding, platelet levels below 50 g/l, presence of petechiae. The heart rate during exercise should not exceed 60-80% of the maximum heart rate. As time passes, the range of exercises may be increased. Activation of movement can be associated with other methods of treatment and it should be applied at least 3 times a week, its duration depending on individual possibilities - 15-60 minutes. Rehabilitation exercises also have a very positive

effect on the reduction of inflammatory parameters and improvement of mood in this group of patients. It may be interesting to examine the effect of physiotherapy on the prolongation of patients' survival. In cancer patients exercising in groups, aerobic exercises called walking programs, exercises with the use of a cycloergometer, walking on a treadmill, dancing are recommended. The use of aerobic exercises in combination with psychotherapy and pharmacological treatment will improve the patients' quality of life, therefore interdisciplinarity and holistic approach to cancer patients should be taken into account [36]. General exercises and movement can therefore have an analgesic effect, raising the level of endorphins. Campbelli's and colleagues' studies clearly show that patients using K. S. Courneyi's warm-up training, exercises lasting 20 minutes, such as: breathing, general fitness, calming, relaxation exercises, have significantly improved their quality of life [37]. It is also extremely important to improve cardiovascular fitness, breathing, digestion, activation of the skeleton system and other systems. Exercises and movement in patients with cancer, as already mentioned, also have an antifracture effect, consisting in reduction of bone resorption in course of the basic disease. The application of exercises is also very important in antifungal prophylaxis, because continuous activation of patients who have undergone surgical procedures, as well as in patients treated conservatively due to lack of physical activity, there is a high level of embolism readiness. The advantage of physiotherapy in case of oncological patients is the fact that they can perform it at home, e.g. aerobic training on a cycloergometer, or by walking. Physiotherapy in case of oncological patients should be controlled by experienced physiotherapists. The need to individualize the admissible forms of physiotherapy and kinesiotherapy should be taken into account. The problem of rehabilitation in cancer patients is still open. It is worth remembering that active exercises, breathing exercises, exercises on a cycloergometer or treadmill are extremely important from the therapeutic point of view. When choosing a specific form of physiotherapy, as has already been said, attention should be paid to the patient's age, gender, course of basic disease, coexisting diseases, the forms of treatment used, the choice of appropriate time and frequency of exercise. During these procedures it is necessary to monitor the clinical condition, mood and adaptability to a specific type of treatments. As it results from the analysis of the described different reactions occurring in terminally ill patients, the disease has a very large impact on the patient's behaviour and quality of life. It leads to the loss of physical and mental strength, lack of sense of security, inability to take any action. It strengthens the sense of uselessness, addiction, deprives the sense of life. It creates various expectations for care and support from other people. An additional burden that increases suffering is a strong pain, serious ailments, a sense of disability, as well as the awareness that it is a burden for other people. Therefore, the role of rehabilitation in the autumn of life of cancer patients is still an open and widely discussed problem. Research on indications for physico- and kinesitherapy in chronically ill patients suffering from cancer during aging and old age is currently being performed.

This article should be treated as the effect of an analysis of available sources, showing various aspects of rehabilitation in palliative and hospice care. Numerous articles from the medical literature have been used in its creation, where extremely important problems related to the issue of modern palliative and hospice care and the role of rehabilitation in this branch of medicine are discussed. We also used our own medical experience, which gives the possibility of wide observation of this group of patients and different methods of their use.

REFERENCES

1. Hately J, Laurence V, Scott A et al. Breathlessness clinics within palliative care settings can improve the quality of life and functional capacity of patients with lung cancer. Palliat Med. 2003;17:410-417.
2. Corner J, Plant H, A'Hern R, Bailey C. Non-pharmacological intervention for breathlessness in lung cancer. Palliat Med. 1996;10:299-305.
3. Polubiński JP, West L. Implementation of a massage therapy program in the home hospice setting. J. Pain Symptom Manage. 2005;1:104-106.
4. Horst R. Trening strategii motorycznych i PNF. Top School, Kraków 2010: 155–167.
5. Krajnik M. Objawy ze strony układu oddechowego. In: De Walden-Gałuszko K. (ed.). Podstawy opieki paliatywnej. Warszawa: PZWL, 2007, 63-64.
6. Fishman AP. Pulmonary rehabilitation research. NIH workshop summary. Am J Respir. Crit. Care Med. 1994;149:825-833.
7. Zieliński J. Epidemiologia. In: Zieliński J, Górecka D, Celiwiński P (eds). Przewlekła obturacyjna choroba płuc. Warszawa: PZWL; 1998, 20-51
8. Lanken PN, Terry PB, DeLisser HM et al. An official American Thoracic Society policy statement: Palliative care for patients with respiratory diseases and critical illnesses. Am J Respir Crit Care Med. 2008;177:912-927.
9. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, American Thoracic Society/ European respiratory society statement on pulmonary rehabilitation. Am J Respiro Crit Care Med. 2006;173:1390-413.
10. Grądalski T, Ochałek K. Podstawy patofizjologii i postępowania w obrzęku limfatycznym w chorobie nowotworowej. Nowa Med. 2001;97:55-58.
11. Ryan M, Stainton MC, Jaconelli C et al. The experience of lower limb lymphoedema for women after treatment for gynecological cancer. Oncol. Nursing Forum 2003; 3:417-423.
12. Brauer WJ, Herpertz U, Schuchardt C, Weissleder H. Therapierichtlinie: Lymphödem – diagnose und therapie. Physikalische Rehabilitationsmedizin Kurortmedizin 2003;13:291-295.
13. International Society of Lymphology. The diagnosis and treatment of peripherial lymphoedema: consensus document of the International Society of Lymphology. Lymphology 2003;36:84-91.
14. Földi M, Strössenreuther R. Grundlagen der manuellen Lymphdrainage. Urban & Fischer, München 2003:38-46.
15. Pyszora A, Graczyk M, Krajnik M, Doś J. Implementation of modified manual lymphoedema treatment – complex physical therapy (MLT-CPT) in terminally ill patient. Adv Palliat Med. 2007;6:93-95.
16. European Wound Management Association (EWMA). Focus Document: Lymphoedema bandaging in practice. MEP Ltd., Londyn 2005.
17. Földi M, Strössenreuther R. Grundlagen der manuellen Lymphdrainage. München: Urban & Fischer, 2003, 38-46.
18. Lewit K. Terapia manualna w rehabilitacji chorób narządu ruchu. Kielce: ZL Natura, 2001; 247-251.
19. Bieda J, Sopata M. Obrzęk chłonny – klasyfikacja, diagnostyka i leczenie. Przegl Flebol. 2004;1:21-27.

20. Cavezzi A, Michelini S. Phlebolymphoedema – from diagnosis to therapy. Bologna: Edizioni P.R., 1999, 137-141.
21. Ryan M, Stainton MC, Jaconelli C et al. The experience of lower limb lymphoedema for women after treatment for gynecological cancer. Oncol Nursing Forum 2003;3:417-423.
22. Larkin P.J., Sykes N.P., Centeno C et al. The management of constipation in palliative care: clinical practicerecommendations. Palliat. Med. 2008;22:796-807.
23. Manheim C. The myofascial release manual. 4th edn. New York: Slack, 2008.
24. Preece J. Introducing abdominal massage in palliative care for the relief of constipation. Compl Ther Nurs Midwifery 2002;8:101-105.
25. Davis MP, Khoshknabi D, Yue GH. Mangement of fatigue in cancer patients. Curr Pain Headache R. 2006;10:260-269.
26. Vogelzang NJ, Breitbart W, Cella D et al. Patient, caregiver and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. Semin Hematol. 1997;34(supl. 2):4-12.
27. Newell S, Sanson-Fisher RW, Girgis A, Bonaventura A. Howwell do medical oncologists' perceptions reflect their patients' reported physical and psychosocial problems? Data from a survey of five oncologists. Cancer 1998;83:1640-1651.
28. Curt GA, Breitbart W, Cella D et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000;5:353-360.
29. Curt A, Breitbart W, Cella D et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000;5: 353-360.
30. Beth Israel Medical Center. Six E's for Managing Fatigue. www.stoppain.org/palliative_care/content/fatigue/default.asp.
31. Berger AM, Abernethy AP, Atkinson A et al. NCCN Practice Guidelines in Oncology – v.1.2008. Cancer-Related Fatigue http://www.nccn.org/professionals/physician_ gls/PDF/fatigue.pdf.
32. Pruszewicz A, Wiskirska-Woźnica B, Walczak M. Zaburzenia połykania – postępowanie diagnostyczne i zasady rehabilitacji. Przew Lek. 2002;9:102-104.
33. Horst R. Trening strategii motorycznych i PNF. Kraków: Top School, 2010, 155-167.
34. Adamsen L, Quist M, Midtgaard C, Andersen T. The effect of a multidimensional exercise intervention on physical capacity, well-being and quality of life in cancer patients undergoing chemotherapy. Support. Care Cancer 2005;14:116-127.
35. Dimeo F, Rumberger BG, Keul J. Aerobic exercise as therapy for cancer fatigue. Med Sci Sports Exerc. 1998;30:475-478.
36. Mock V, Dow KH, Meares C et al. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. Oncol Nurs Forum 1997;24:991-1000.
37. Campbell A, Mutrie N, White F et al. A pilot study of a supervised group exercise programme as a rehabilitant treatment for women with breast cancer receiving adjuvant treatment. Europ J Oncol Nurs. 2005;9:56-63.

Conflict of interest:
All authors daclare no conflict of interest.

CORRESPONDING AUTHOR
Ewa Kucharska
e-mail: ewa.kucharska@vadimed.com.

Received: 26.03.2019
Accepted: 24.05.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES OF TISSUE HOMEOSTASIS IN PATIENTS WITH ALOPECIA AREATA IN THE CHRONIC STAGE ASSOCIATED WITH METABOLIC SYNDROME AND THE NON-BURDENED COURSE OF THE DISEASE

Svitlana V. Vozianova, Olena O. Dyadyk, Inna I. Horda, Yaroslav S. Radkevich
SHUPYK NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KYIV, UKRAINE

ABSTRACT

Introduction: Alopecia areata (AA) is a tissue-specific disease of the hair follicles, manifested by foci of baldness on the head and other areas of the skin.

The aim of the study was to identify the tissue homeostasis state on the basis of pathomorphological and immunohistochemical changes taking into account the features of Ki67, bcl-2, caspase-3, and CD31 expression in patients with AA in the chronic stage associated with metabolic syndrome and the non-burdened course of the disease.

Materials and methods: Pathomorphological and immunohistochemical studies of Ki67, bcl-2, caspase-3, and CD31 expression in biopsies specimens from skin lesions in the chronic stage of the disease were performed in 11 patients with AA associated with metabolic syndrome and the non-burdened course of the disease.

Results: The results of complex morphological study showed that in skin biopsies of patients with AA with metabolic disorders pathomorphological changes were more affected both in the epidermis and skin appendages – degenerative changes in the epithelium, in the dermis, manifestations of appendage atrophy and stromal fibrosis. In patients with AA without metabolic disorders the proliferative potential of epithelial cells (Ki67 proliferation index) was 20–25%, in cases of AA with metabolic syndrome – 5–10%, indicating a decrease in regenerative capacity of the tissue. The state of the microcirculatory bed (CD31) in cases of AA without metabolic disorders is more favorable for the trophic tissue function and decreases in the group of AA with metabolic disorders. It was found that activation of pathological cell apoptosis was observed in cases of AA with metabolic disorders and lower level of bcl-2 expression. In our observations, the level of expression of caspase-3 was at a relatively high level, indicating the activation of pathological apoptosis in the tissues of the affected areas.

Conclusions: Our pathomorphological, immunohistochemical data allows us to assert that it is advisable to carry out a biopsy of the affected areas with the establishment of levels of proliferative activity of epithelial and stroma cells, the state of the microcirculatory vessels, the possibilities of repair of the affected areas, assessment of the level of apoptosis in order to predict the course of the disease and usage of the personified approach to treatment.

KEY WORDS: alopecia areata, pathomorphological and immunohistochemical studies, metabolic syndrome

Wiad Lek 2019, 72, 7, 1236-1242

INTRODUCTION

Alopecia areata (AA) is a tissue-specific disease of the hair follicles, manifested by foci of baldness on the head and other areas of the skin. AA is the most common autoimmune disease with non-pubescent type of hair loss. According to demographic studies, at least 1–2% of the total population suffers from alopecia areata once during the lifetime [1]. The lack of effective universal methods for treating patients with AA, due to insufficient understanding the aetiology, pathogenetic mechanisms of the disease, pathomorphological changes in anagen hair follicles (HF), indicates the relevance of the study of this pathology.

Studies of the last decade show that alopecia can be associated with a metabolic syndrome with a high risk of development in such a group of patients with cardiovascular diseases [2]. According to M. Hanefeld, about 15% of people from 40 to 75 years old have a metabolic syndrome [3].

According to international recommendations in the clinical practice the diagnosis of "metabolic syndrome" includes disorders of glucose tolerance or type II diabetes, abdominal type of obesity, dyslipidemia, arterial hypertension, microalbuminuria and a tendency to rapid progression of atherosclerosis and its complications. Clinical polymorphism, metabolic disorders, morphological and immunohistochemical changes in affected areas, which reflect the features of tissue homeostasis in this disease, must be considered in order to develop an algorithm for effective treatment of patients with AA.

THE AIM

The aim of the study was to identify the state of tissue homeostasis on the basis of pathomorphological and

immunohistochemical changes taking into account the level of cell proliferation, differentiation and apoptosis considering the features of Ki67, bcl-2, caspase-3, and CD31 expression in patients with AA in the chronic stage associated with metabolic syndrome and the non-burdened course of the disease.

MATERIALS AND METHODS

Clinical and laboratory examination of 30 patients with different clinical forms of AA was conducted. In order to determine the metabolic syndrome, clinical and laboratory diagnosis was performed: general clinical laboratory examination (common blood test, common urine test) and biochemical examination with determination of blood glucose, cholesterol, glycated hemoglobin, total bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, total protein, thyrotropic hormone, free thyroxine, thyroperoxidase antibodies, high density lipoproteins, low density lipoproteins, triglycerides, C-peptide, HOMA index. Performed functional (indicators of blood pressure, pulse) and anthropometric (indicators of height, weight, body mass index, waist circumference) measurements. Dermatoscopy was performed using a computer diagnostic program and Aramo SG video dermatology equipment (Korea).

Morphological studies of Ki67, bcl-2, caspase-3, and CD31 expression in biopsies specimens from skin lesions in the chronic stage of the disease were performed in 11 patients with chronic AA (in 6 patients associated with metabolic syndrome and in 5 patients with non-burdened course of the disease).

All patients, with their consent, were taken panch-biopsy from the center of skin lesions under local infiltration anesthesia. In the morphological study, the biopsies were fixed in 10% neutral buffered formalin solution (pH 7.4) for 24-36 hours, the material was carried out according to the standard procedure, poured into paraffin, sections with thickness of 4-5 microns were stained with hematoxylin and eosin. In all cases immunohistochemistry (IHC) with monoclonal antibodies (MAB) to Ki-67 (clone SP6), BCL-2 (clone 1034P12), CD31 (clone 1035P4), and caspase-3 (clone 74T2) was performed in order to determine the proliferative activity, apoptosis level and vessel state. During the IHC there was used an Ultra Vision Quanto HRP Detection System, the chromosome DAB Quanto (Thermo Fisher Scientific (the USA)) [4, 5]. Microscopic examination and photoarchivision were performed using ZEISS optics microscopes (Germany) with the "Axio Imager. A2" data processing system with magnifying lenses 5x, 10x, 20x, 40x, binocular nozzle 1.5 and glasses 10 with camera ERc 5s "Carl Zeiss" Primo Star with Camera Axiocam105 color. The marker expression was evaluated using a semi-quantitative method.

Statistical processing of the results obtained was carried out on a personal computer in the program "STATISTICA 10 for Windows".

RESULTS

30 patients with different clinical forms of AA were under our supervision. In 16 patients AA was associated with a metabolic syndrome, and in 14 patients it was associated with non-burdened course of the disease. The average age of patients was 30.6±0.9 years (18-60 years); men – 8, women – 22. In all patients the chronic stage of AA was confirmed both by clinical (absence of hair growth in the areas of baldness and the zone of shaky hair at the periphery of the foci, unchanged skin) and dermatological symptoms (lack of dystrophic hair in the form of an exclamation mark and black dots, cadaverized hair, small amount yellow dots and vellus hair).

In order to standardize the assessment of hair loss and optimize the monitoring of patients with AA, we used the SBN international scale which takes into account the standard definition of the percentage of hair loss according to the criteria: S (scalp), B (body), possible nail defect, N (nail).

The range of the criterion S (scalp): S0 – no hair loss; S1 – loss of <25% of hair; S2 – loss of 25-49% of hair; S3 – loss of 50-74% of hair; S4 – loss of 75-99% of hair; S5 – loss of 100% of hair.

A complete examination of the patient's body hair was required to determine criterion B (body), including the skin of face, torso, extremities, inguinal areas and genitals: B0 – no hair loss on the body; B1 – partial loss of body hair; B2 – loss of 100% of body hair.

To determine possible dystrophic changes in nails in patients with AA, the criterion N (nail) was determined: N0 – no nail defects; N1 – some degree of nail defects; N2 – dystrophy of 20 nails (trachiochiasis).

According to severity of AA in the group with non-burdened course of disease patients were distributed as follows: 6 patients with the phenotype S1, 5 patients with the phenotype S2-S3, 3 patients with the phenotype S4-S5. In the group of patients with AA associated with metabolic syndrome 5 patients had mild form of disease (S1), 7 patients had moderate to severe form (S2-S3) and 4 patients had severe form (S4-S5).

In order to determine the features of morphological and immunohistochemical changes in the skin of patients with AA associated with metabolic syndrome and with non-burdened course of the disease, the study was conducted in comparable groups for the severity of the disease (S2-S3). The model S2-S3 takes into account the loss of up to 50% of hair and is considered as a moderate form of the disease.

During morphological investigation all cases were divided into two groups: "group A", which included patients with chronic AA with non-burdened course of the disease and "group B", a group of patients with metabolic syndrome. Studies of these groups was divided into two phases, in the first phase the histological sections were studied with standard hematoxylin and eosin staining to identify common pathological processes in the skin and its appendages. In the second phase the IHC was conducted with the assessment of their availability, the nature of the antibodies expression, namely its localization prevalence and intensity of color.

In the "group A" during hematoxylin and eosin staining the epidermis was unevenly thickened, there were manifestations of hyperkeratosis, deep epidermis departments with signs of intracellular edema and foci of degenerative changes in the type of dystrophic. In the dermis, the number and size of the dermal papilla (fig. 1) were increased, there were cells of lympho-histiocytic infiltration with isolated eosinophilic leukocytes around the hair follicle, sebaceous, sweat glands and perivascular. Hair follicles with manifestations of atrophy, the outer and inner root sheathes were peeled with signs of cell apoptosis. Volume of sebaceous glands was increased with minor fibrous changes around (fig. 2).

During conducting IHC with MAB to Ki67, pronounced proliferative activity in the deep layers of the epidermis, which is represented by groups of positive cells with a dense location (fig. 3) and focal proliferation in the epithelial component of the follicular bag (fig. 4), is noted. The general proliferative index reaches 20-25%.

IHC with MAB to CD31 exhibits positive expression of endothelial cells and practically continuous cell groups in the epidermal-dermal region with a colour intensity of +++, which characterizes the active regenerative capacity of blood vessels of the microcirculatory system (fig. 5).

Evaluating the expression of the anti-apoptotic protein bcl-2, attention is paid to the moderate intensity of coloration of individual cells around the skin appendages, namely around degeneratively changed hair follicles, along with this a pronounced positive reaction in the epidermis with the intensity of coloration +++, which almost completely fills 2/3 of the layer thickness (fig. 6).

The level of caspase-3 expression in the epidermis and in the epithelial component of the appendages of the skin varied from moderate (++) to the expressed (+++); also, individual positive cells in the dermis are visualized (fig. 7, 8).

In the morphological study of the cases from "group B" with hematoxylin and eosin staining uneven thickening of the epidermis, areas of hyper- and parakeratosis, marked degenerative and apoptotic changes in the epidermis, signs of intracellular edema were observed. In the dermis there were areas with a smoothed pattern of papillary layer (fig. 9), focal sclerosis of the epidermal-dermal connection, focal lympho-histiocytic infiltration around the appendages and perivascular.

In separate hair follicles, the bulb was replaced by keratinous detritus, perifollicular growth of connective tissue was observed. Presented hair follicles with manifestations of atrophy, external and internal root sheathes were removed with inflammatory infiltration. There were fragments of sweat glands with pronounced focal fibrosis (fig. 10).

Comparing the proliferative activity with the previous "group A" during the IHC with MAB to Ki-67, there is a marked reduction in the expression by the epidermis cells, which are single cells in the basal unit (fig. 11), decreased activity in the epithelial component of the skin appendages that can be observed also in the walls of the sebaceous glands (fig. 12). The general proliferative index is 5-10%.

IHC with MAB to CD31 exhibits pronounced positive expression in vascular endothelial cells, moderately pronounced expression in single and separate cells in the dermis (fig. 13). This pattern of cell placement and density with positive expression indicates a violation of the compensatory and adaptive changes in the microcirculatory system to the processes of regeneration in contrast to the observations in the "Group A".

Similar tendency of uniform decrease of expression is observed also at carrying out of ICH with MAB to bcl-2 (fig. 14).

The level of expression of caspase-3 corresponds to moderate in structural units of the appendages of the skin (fig. 16) and pronounced expression in the cells of the epidermal layer (fig. 15).

DISCUSSION

AA is an autoimmune tissue-specific disease. The limit of the inflammatory process, which is formed around the anagen hair follicles in the form of regional intra- and perifollicular pathology, determines its tissue-specific nature [6, 7].

The pathogenesis of the disease involves immune regulatory cells that are responsible for peripheral tolerance [8-10]. Perifollicular inflammation initiates a violation of the tissue homeostasis of the hair follicle, as a result of this process, a gradual discontinuation of hair growth occurs.

Co-operation of CD8 + cytotoxic T lymphocytes with CD4 + T helper cells, CD68 + macrophages and Langerhans cells in peri- and intrafollicular infiltration, as well as hyperproduction of IL-2, TNFα, and IFγ inflammatory cytokines, induces premature telogen and inhibits the hair growth [1, 11]. Study of the role of CD25 / IL-2Rα receptor modulation in AA foci may allow the detection of prolonged persistence of cytotoxic lymphocytes in tissues [12, 13].

Causes of dysmorphogenesis of hair follicles are not sufficiently studied. In recent years, more and more scientific studies have been published, in which the connection of the development of AA and metabolic disorders in the body is revealed.

In comparable groups of patients with AA without metabolic syndrome (group A) and groups of patients with AA with metabolic syndrome (group B) with a standard hematoxylin and eosin staining, we found that in skin biopsies in patients with metabolic disorders, pathological changes are more pronounced – they appear both from the epidermal component and the appendages of the skin. In the epidermis there were more pronounced degenerative changes; in the dermis, appendages of skin - manifestations of atrophy and fibrosis of the stroma.

According to the literature, in the active stage of AA, the nature of impairments in the HF is associated with the termination of cell differentiation processes, reduced cell proliferation, which is manifested as a decrease in the number of Ki67 + -cells; apoptosis has a pronounced character. In the chronic stage in the matrix zone of the HF, in the region of the dermal papilla, bcl-2 is detected in cells that are absent in the active stage of the disease. Also, an extension of the cell proliferation

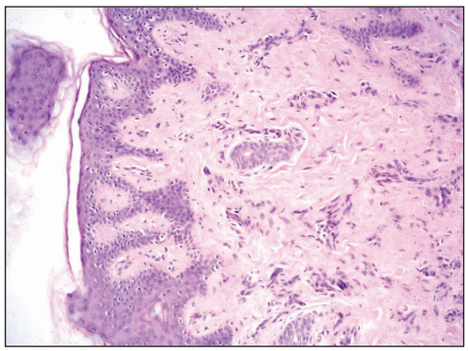


Fig. 1. Group A. A fragment of the skin with uneven thickening of the epidermal layer, thickening of the dermal papillaes and dystrophic changes, focal stromal fibrosis. Stained with hematoxylin and eosin, × 100.

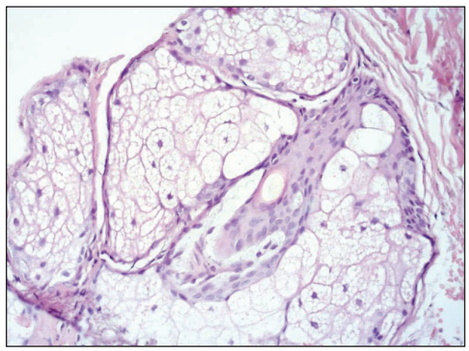


Fig. 2. Group A. Fragment of the enlarged sebaceous gland, periglandular minor fibrosis. Stained with hematoxylin and eosin, × 100.

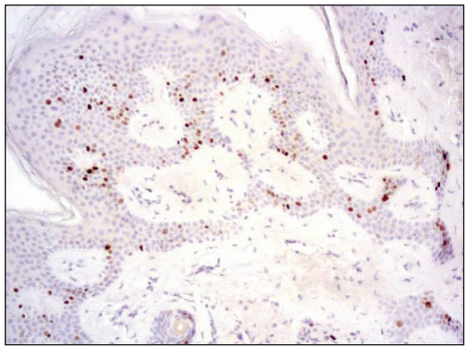


Fig. 3. Group A. Detection of groups of positively colored cells with pronounced intensity in the deep epidermis. IHC with MAB to Ki-67, × 100.

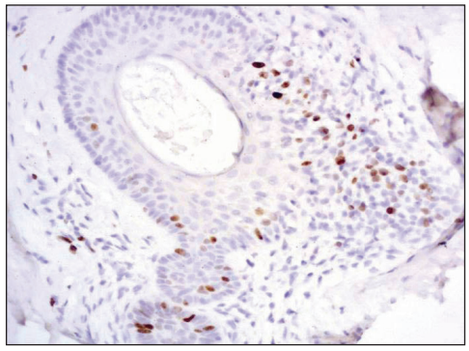


Fig. 4. Group A. Positive nuclear cell expression in the epithelial component of the focal hair follicle bulb. IHC with MAB to Ki-67, × 200.

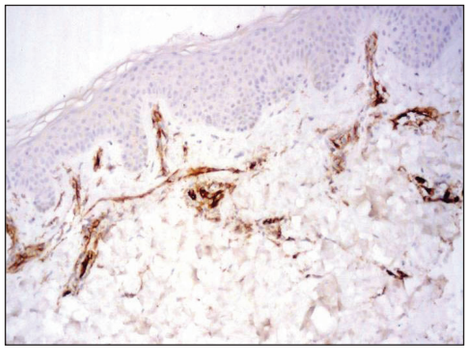


Fig. 5. Group A. Pronounced expression by the endothelium cells of the microcirculatory vesseles, including in the epidermal-dermal zone. IHC with MAB to CD31, × 100.

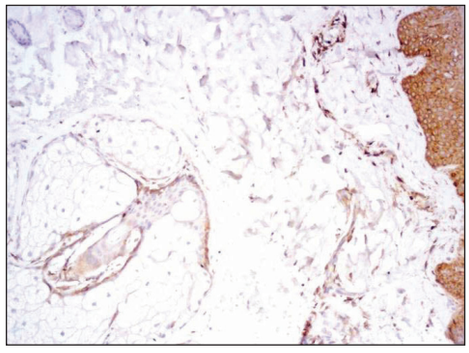


Fig. 6. Group A. Pronounced expression of bcl-2 by cells of epidermal layer, moderate expression of bcl-2 around the hair follicle. IHC with MAB to bcl-2, × 100.

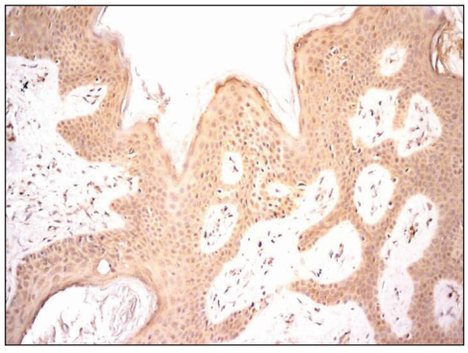


Fig. 7. Pronounced expression in cells of the epidermis of the affected area. IHC with MAB to caspase-3, × 100.

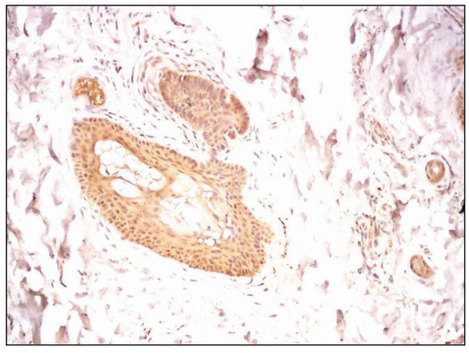


Fig. 8. Pronounced expression in the epithelial component of the appendages of the skin. IHC with MAB to caspase-3, × 100.

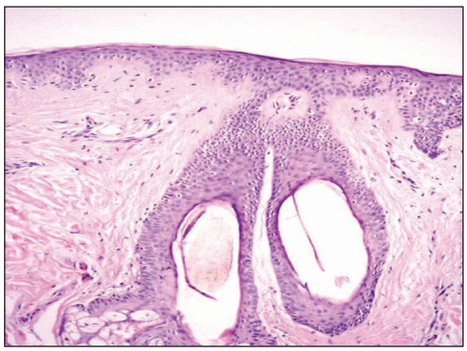


Fig. 9. Group B. A fragment of the skin with signs of epidermis atrophy, degenerative changes in the epithelial component, edema, dysmucoidosis and focal stromal fibrosis. Stained with hematoxylin and eosin, × 100.

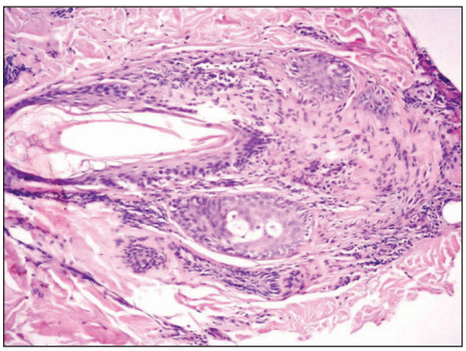


Fig. 10. Group B. A fragment of the skin with pronounced fibrous changes around the appendages of the skin and focal lympho-histiocytic infiltration, keratin detritus partially fills the hair follicle. Stained with hematoxylin and eosin, × 100.

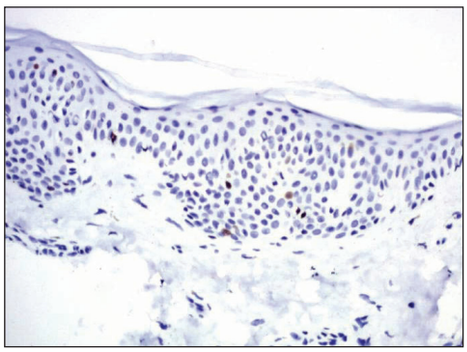


Fig. 11. Group B. Expression of single, positively coloured cells in the epidermis. IHC with MAB to Ki-67, × 200.

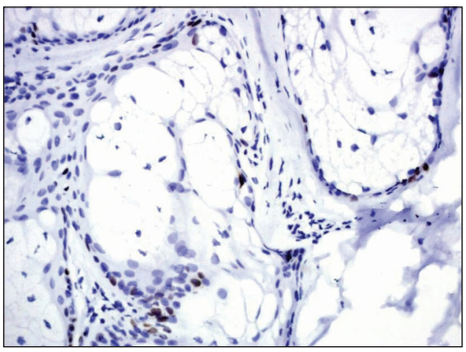


Fig. 12. Group B. Single, positively coloured cells in the epithelium of the sebaceous glands. IHC with MAB to Ki-67, × 200.

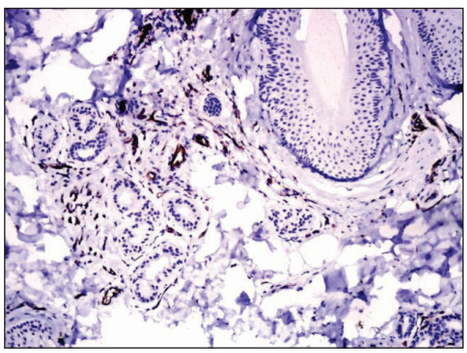


Fig. 13. Group B. Pronounced expression by the cells of the endothelium of the vessels and isolated individual cells in the dermis. IHC with MAB to CD31, × 100.

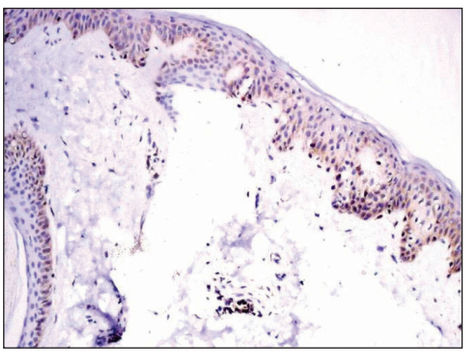


Fig. 14. Group B. Moderately-mildly pronounced expression in the cells of the epidermal layer, and in the epithelium of the hair follicle. IHC with MAB to bcl-2, × 100.

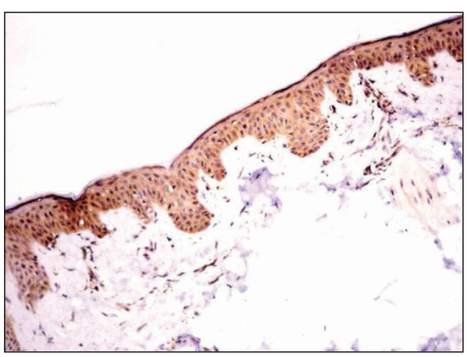


Fig.15. Pronounced expression in the epidermis of the affected area. IHC with MAB to caspase-3, × 100.

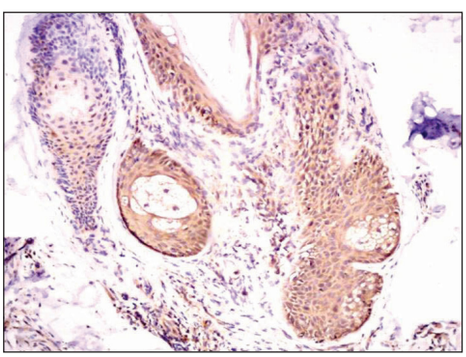


Fig.16. Moderate expression in the cells of the appendages of the skin of the affected area. IHC with MAB to caspase-3, × 100.

zone in the infundibular region is noted. We assessed the proliferative potential of epithelial cells – the level of proliferative activity using Ki67, based on the performed IHC. In group A it was 20–25%, whereas in group B it was 5–10%, which indicates a decrease in regenerative, reparative capacities of tissues in patients with AA with a metabolic syndrome, which coincides with the given literature data.

Recent studies have shown that the state of tissue homeostasis in healthy anagenic HF is supported by the balance between processes of proliferation, differentiation and apoptosis of cells with the participation of the anti-apoptotic protein bcl-2, which is detected in cells of the matrix zone of HF. The IHC study conducted by us allowed us to evaluate the peculiarities of expression of the anti-apoptotic protein bcl-2 and to establish that the level of expression in the group of patients with AA and metabolic disorders was significantly lower than in the group of patients with AA without metabolic disorders, which indicates the activation of pathological apoptosis of cells in the "group B". Along with this, the study of the level of expression of caspase-3 showed no difference in the studied groups, was at a relatively high level, indicating the activation of pathological apoptosis in the tissues of the affected areas in patients with AA in the stationary phase.

In addition to the aforementioned component of pathogenesis in the development of AA, the important role is played by the Fas FasL pathways of apoptosis of HF cells formed in conditions of cellular immune regulation in the absence of anti-apoptotic protein bcl-2 in HF cells and regulatory CD25/IL2Rα + -T-cells of the dermis [14, 15].

Taking into account the importance of the regenerative potential of the affected tissues, we estimated the prevalence and level of CD31 expression. The obtained data allowed to assert that in cases of AA without metabolic disorders, the state of the microcirculatory vessel is more favourable for the trophic function of tissues, which contributes to the reparative capabilities of the affected tissues. In the AA monitoring group with metabolic disorders, the level of CD31 expression significantly decreased, and the number of vessels in the microcirculatory vessel decreased, that is, the conditions for repair/regeneration of the affected structures in this group were significantly lower.

CONCLUSIONS

The obtained pathomorphological, immunohistochemical data of the features of tissue homeostasis in patients with AA in the stationary stage, allow us suggesting that in the case of prediction of the course of the disease and the use of a personified approach to treatment, it is advisable to conduct biopsy of affected areas with the establishment of levels of proliferative activity of epithelial cells, to assess the state of microcirculatory vessels, possibilities of reparation of affected areas, to assess the level of apoptosis.

PERSPECTIVES FOR FURTHER DEVELOPMENTS

Further studies are aimed at determining the correlation between clinical, pathomorphological and immunohistochemical indicators in order to improve treatment and predict the course of the disease.

REFERENCES

1. Alkhalifah A, Alsantali A, Wang E et al. Alopecia areata update: Part I. Clinical picture, histopathology and pathogenesis. Journal of the American Academy of dermatology. 2010; 62(2):177-188.
2. Abramovits W., Losornio M. Failure of two ETA-alpha blockers to influence the course of alopecia areata. Skinmed. 2006; 5(4):177-181.
3. Chiasson J.L., Josse R.G., Gomis R. et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance the STOP-NIDDM trial. Journal of the American Medical Association. 2003; 290:486-494.
4. Petrov S.V., Raykhlin N.T. Rukovodstvo po immunohistokhimicheskoj diagnostike opukholej cheloveka [Guide for immunohistochemical diagnosis of human tumors]. Kazan, 2012:612. (Ru)
5. Griffin G., Treanor D. Digital pathology in clinical use: where are we now and what is holding us back? Histopathology 2017; 70 (1): 134-145.
6. Gilhar A., Kalish R.S. Alopecia areata: a tissue specific autoimmune disease of the hair follicle. Autoimmunity Reviews. 2006; 5: 64-69.
7. Gilhar A., Paus R., Kalish R.S. Lymphocytes, neuropeptides and genes involved in alopecia areata. Journal of Clinical Investigation. 2007; 117:2019-2027.
8. Abou Rahal J., Kurban M., Kibbi A.G., Abbas O. Plasmacytoid dendritic cells in alopecia areata: missing link? Journal of the European Academy of Dermatology and Venereology. 2016; 30:119-123.
9. Simpson E. A historical perspective on immunological privilege. Immunological Reviews. 2006; 213:12-22.
10. Tosti A., Piraccini B.M. Diagnosis and treatment of hair disorders. London: Taylor&Francis, 2006; 1:59.
11. McElwee K.J., Freyschmidt-Paul P., Hoffmann R. et al. Transfer of CD8(+) cells induces localized hair loss whereas CD4(+)/CD25(-) cells promote systemic alopecia areata and CD4(+)/CD25(+) cells blockade disease onset in the C3H/HeJ mouse model. Journal of Investigative Dermatology. 2005; 124(5):947-957.
12. Dabbs D. Diagnostic Immunohistochemistry. 4th ed. Philadelphia: Churchill Livingstone; 2014:960.
13. Bodemer C., Pechmaur M., Fraitaig S. et al. Role of cytotoxic T-cells in chronic alopecia areata. Journal of Investigative Dermatology. 2000; 114(1):112-116.
14. Gardzhigoroeva A.G., Kogan E.A., Potekaev N.N. et al. Sootnoshenie protsessov apoptoza, proliferatsii, neoangiogeneza i kletochnoy differentsirovki pri immunnom vospalenii v ochagah gnezdnoy alopetsii. [Relative significance of apoptotic and proliferative processes, neoangiogenesis, and cellular differentiation for immune inflammation at sites affected by circumscribed alopecia]. Klinicheskaya dermatologiya i venerologia. 2010; 2:25-34. (Ru)
15. Freyschmidt-Paul P., McElwee K.J., Botchkarev V. et al. Fas-deficient C3.MRL-Tnfrsf6(lpr) mice and Fas ligand-deficient C3H/HeJ-Tnfsf6(gld) mice are relatively resistant to the induction of alopecia areata by grafting of alopecia areata-affected skin from C3H/HeJ mice. Journal of Investigative Dermatology Symposium Proceedings. 2003; 8:104-108.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Olena O. Dyadyk
Pathological and Topographic Anatomy Department
Shupyk National Medical Academy of Postgraduate Education
9 Dorohozhytska str., Kyiv 04112, Ukraine
e-mail: pathologNew@ukr.net

Received: 15.03.2019
Accepted: 18.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

PREDICTORS OF INAPPROPRIATE SHOCKS FROM IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

CZYNNIKI PRZEPOWIADAJĄCE NIEADEKWATNY CHARAKTER WYŁADOWAŃ WSZCZEPIONEGO KARDIOWERTERA DEFIBRYLATORA

Dariusz Jagielski[1], Dorota Zyśko[2], Klaudiusz Nadolny[3,4], Joanna Wizowska[2], Bartosz Biel[1], Waldemar Banasiak[1], Piotr Ponikowski[1,5]

[1]DEPARTMENT OF CARDIOLOGY, CENTRE FOR HEART DISEASES, 4TH MILITARY HOSPITAL, WROCLAW, POLAND
[2]DEPARTMENT AND CLINIC OF EMERGENCY MEDICINE, WROCLAW MEDICAL UNIVERSITY, WROCLAW, POLAND
[3]DEPARTMENT OF EMERGENCY MEDICINE, BIAŁYSTOK MEDICAL UNIVERSITY, BIALYSTOK, POLAND
[4.]UNIVERSITY OF STRATEGIC PLANNING IN DABROWA GÓRNICZA, DABROWA GORNICZA, POLAND
[5]DEPARTMENT OF HEART DISEASES, WROCLAW MEDICAL UNIVERSITY, WROCLAW, POLAND

ABSTRACT

Introduction: Inappropriate shocks in patients with an implantable cardioverter-defibrillator (ICD) are associated with significant psychological and physical consequences and increased long-term mortality.

The aim: To assess predictors associated with inappropriate high-energy discharges of implantable cardioverter-defibrillators.

Material and Methods: Retrospective data analysis of 150 patients aged 64.2±12.8 years (84.7% male) admitted to the Hospital Emergency Department due to at least one cardioverter-defibrillator discharge was performed. All of the discharges were inappropriate in the group of 33 patients, and in the group of 117 patients at least one discharge was appropriate. The following data: age, gender, concomitant diseases, type of ICD implantation (primary vs. secondary prevention), type of discharge, number of discharges, serum potassium, and sodium concentration were collected.

Results: Patients with only inappropriate discharges were younger, significantly more often had chronic atrial fibrillation, a significantly higher number of discharges, and ischaemic cardiomyopathy. Logistic regression analysis revealed that the occurrence of only inappropriate discharges was related to the number of discharges over three, the age of patients below 60 years, the serum sodium concentration between 135 mEq/L and 142 mEq/L, and the primary type of prevention of sudden cardiac death.

Conclusions:

1. Predictors of inappropriate discharges include: age, serum sodium concentration, and primary type of indications for cardioverter-defibrillator implantation.
2. Further research is necessary to determine the influence of disturbances in the sodium economy on the occurrence of appropriate and inappropriate interventions of implantable cardioverter-defibrillators.

KEY WORDS: implantable cardioverter-defibrillator, inadequate shock, Emergency Department

STRESZCZENIE

Wstęp: Nieadekwatne wyładowania u pacjentów z wszczepionymi kardiowerterami defibrylatorami są związane z istotnymi psychicznymi i fizycznymi działaniami niepożądanymi oraz ze zwiększoną śmiertelnością odległą.

Cele pracy: Ocena jakie czynniki predykcyjne związane są z wstąpieniem nieadekwatnych wyładowań kardiowertera defibrylatora.

Materiał i metody: Retrospektywna analiza danych 150 pacjentów w wieku 64,2 ± 12,8 roku, w tym 84,7% mężczyzn, przyjętych na Szpitalny Oddział Ratunkowy z powodu co najmniej jednego wyładowania kardiowertera defibrylatora. Wszystkie wyładowania były nieadekwatne w grupie 33 pacjentów, a w grupie 117 co najmniej jedno wyładowanie było adekwatne. Zbierane dane: wiek, płeć, choroby współistniejące, charakter prewencji, rodzaj wyładowań, liczba wyładowań, osoczowe stężenie sodu i potasu.

Wyniki: Pacjenci z jedynie wyładowaniami nieadekwatnymi byli młodsi, istotnie częściej mieli utrwalone migotanie przedsionków, mieli istotnie większą liczbę wyładowań oraz kardiomiopatię niedokrwienną. W analizie regresji logistycznej wykazano, że z występowaniem jedynie wyładowań nieadekwatnych powiązana była liczba wyładowań ponad 3, wiek pacjentów poniżej 60 lat, stężenie sodu między 135 mEq/L a 142 mEq/L, pierwotny charakter prewencji nagłego zgonu sercowego.

Wnioski:

1. Do czynników predykcyjnych wyładowań nieadekwatnych należy wiek, stężenie sodu w osoczu, pierwotny charakter wskazań do wszczepienia kardiowertera defibrylatora.
2. Dalsze badania są konieczne dla określenia roli zaburzeń gospodarki sodowej w występowaniu adekwatnych i nieadekwatnych interwencji kardiowertera defibrylatora.

SŁOWA KLUCZOWE: Wszczepialny kardiowerter defibrylator, nieadekwatne wyładowanie, oddział ratunkowy

INTRODUCTION

Implanted cardioverter defibrillator (ICD) devices are used to reduce the arrhythmia-related risk of sudden cardiac death mainly in patients with advanced left ventricular dysfunction [1]. The number of admissions of ICD patients to Emergency Departments due to high-energy therapy is increasing [2]. Inappropriate shocks occur in about 11% of implanted patients [3]. These unnecessary shocks do not save lives and have a negative impact on patients. The shocks are associated with significant psychological and physical adverse effects and may increase the patients' mortality [4]. Most inappropriate shocks are related to a fast ventricular rate during atrial fibrillation; however, fast sinus rhythm, supraventricular tachycardia, oversensing caused by lead fracture, T-wave sensing (double counting), and electromagnetic interference may also lead to ventricular arrhythmia recognition by the ICD and may result in high-energy therapy delivery [4]. The presence of ICD shocks reflects more advanced cardiac disease. However, the reduction of ICD shocks may reduce cardiovascular mortality [5]. Shocks may result in increased myocardial damage and inflammation [6]. The first-line method to decrease the number of inappropriate shocks is ICD reprogramming. Beta-blockers can also reduce the number of inappropriate shocks. However, inappropriate shocks may still occur. Therefore, gaining knowledge about the factors associated with inappropriate discharges may be important for further attempts to prevent their occurrence.

THE AIM

The aim of the study was to find predictors of inappropriate shocks in patients admitted to Emergency Departments due to high-energy ICD therapy.

MATERIAL AND METHODS

A retrospective analysis of the medical records of ICD patients admitted to the Emergency Department due to high-energy ICD therapy, for whom the medical records included information about the appropriateness of the shocks.

The following data were gathered: age, gender, number of shocks during the last 24 hours, appropriateness of the shocks, left ventricular ejection fraction, concomitant diseases, and type of sudden cardiac death prevention: primary or secondary.

The patients were divided into two groups: Group 1 with only inappropriate shocks and Group 2 with appropriate shocks. The patients with both types of therapy were included in Group 2.

STATISTICAL ANALYSIS

The continuous variables were presented as means and standard deviations or medians and interquartile ranges and were compared using Student's t-test or the Mann-Whitey U-test, as appropriate. Discrete variables were presented as numbers and percentages and compared using the chi-squared test

Because some variables may have non-linear association with the outcome, the nonlinear method – Classification and Regression Trees (CART) analysis – was used to find cut-off points. CART analysis was performed for serum sodium and potassium concentrations and shock numbers. Logistic regression analysis was used to find the association between the dependent variable: inappropriate shocks only and the independent variables: 1. age above 60 years, 2. the variables that differ in univariate analysis, 3. sodium and potassium concentration and shocks number cut-off points obtained from CART analysis.

RESULTS

Group 1, were patients of which had only inappropriate shocks, consisted of 33 patients (22%) whereas Group 2, were patients of which had appropriate or appropriate and inappropriate shocks, consisted of 117 patients (78%). The patients with only inappropriate shocks constituted a significantly lower percentage of patients compared to those with appropriate shocks ($p < 0.001$).

A comparison of the two groups of patients is presented in Table 1.

Patients in Group 1 were younger, had higher heart rate of chronic atrial fibrillation, and a higher number of shocks.

The cut-off points for serum sodium concentration for the appropriate shock prediction were less than 135 mEq/L and more than 142 mEq/L. The cut-off point for serum potassium concentration for the appropriate shocks were less than 3.45 mEq/L and more than 5.1 mEq/L.

Stepwise regression analysis revealed that a number shocks higher than three increases the chances of inappropriate shock occurrence, whereas age older than 60 years, sodium dichotomised less than 135 mEq/L or more than 142 mEq/L, and sudden cardiac death secondary prevention increases the chances for at least one appropriate shock.

DISCUSSION

We have found that simple clinical and laboratory data could predict the appropriateness of ICD shocks in patients admitted to Emergency Departments due to high-energy ICD therapy. The finding that younger age is related with inappropriate shocks is concordant with the reports of other authors [7, 8]. Olde Nordkamp et al. reported in a population with mean age 39 years an annual rate of inappropriate shocks of approximately 5% [7]

The association between younger age and inappropriate shocks may be related with higher incidence of activities leading to increased sinus rhythm in younger groups, such as playing sport, quarrels, or fighting.

The significance of increased heart rate on the occurrence inappropriate shocks was indicated in studies showing that inappropriate shocks are related with underuse of beta-blockers [8]

In the presented study paroxysmal atrial fibrillation was more prevalent in patients with inappropriate shocks only.

Table 1. Demographics and clinical data

	Group 1 N = 33	Group 2 N = 117	p
Age (years)	58.7±11.8	65.7±12.7	0.005
Male gender - n (%)	30 (90.9)	97 (82.9)	0.26
Secondary prevention - n (%)	8 (24.2)	52 (44.4)	0.036
Median number of shocks (interquartile range)	6 (4-8)	2 (1-4)	0.002
Chronic atrial fibrillation - n (%)	17 (51.5)	34 (29.1)	0.018
Paroxysmal atrial fibrillation - n (%)	10 (30.3)	40 (34.2)	0.67
Diabetes - n (%)	8 (24.2)	36 (30.8)	0.47
Myocardial infarction - n (%)	30 (46.1)	67 (56.3)	0.28
Non-ischaemic cardiomyopathy - n (%)	13 (39.4)	30 (25.6)	0.12
Ischaemic cardiomyopathy - n (%)	15 (45.5)	79 (67.5)	0.02
Reason for ICD implantation other than ischaemic or non-ischaemic cardiomyopathy - n (%)	5 (15.2)	8 (6.8)	0.13
Thyroid disease - n (%)	5 (15.1)	21 (17.9)	0.95
Left ventricular ejection fraction [%] mean±SD	36.0±13.3	32.2±13.0	0.14
Serum sodium concentration	138.9±2.4	138.1±4.2	0.31
Serum potassium concentration	4.0±0.5	4.0±0.6	0.72

Table 2. Logistic regression analysis. Dependent variable - only inappropriate shocks

	Age > 60	Sodium > 142 mEq/L or less than 135 mEq/L	More than 3 shocks	Secondary prevention
OR	0.30	0.16	11.14	0.33
- 95% CI	0.11	0.03	3.89	0.12
+ 95% CI	0.81	0.80	31.85	0.91
p	0.017	0.026	0.001	0.033

However, in multivariate analysis this variable was not an independent factor. Paroxysmal atrial fibrillation usually leads to many ICD discharges because the pain related to ICD shock causes a further increase in ventricular rate. Moreover, paroxysmal atrial fibrillation more often occurs in younger patients; therefore, this variable may be "hidden" in variables such as age and number of shocks higher than three

Secondary prevention of sudden cardiac death was related to appropriate shock occurrence. This finding is concordant with studies of other authors [9-11]. The patients with a cardioverter-defibrillator implanted for secondary prevention had in their medical history ventricular arrhythmias that could provoke ICD shocks. These patients had proven their susceptibility to ventricular arrhythmias. Therefore, it is not strange that they had increased risk for ventricular arrhythmia relapse

The most intriguing finding is that sodium level lower than 135 mEq/L or higher than 142 mEq/L is related to appropriate shock occurrence. Decreased sodium level is a marker of heart failure progression, which in turn is a risk factor for ventricular arrhythmia and appropriate shock. Moreover, it could be considered that sodium channel blockade is an approved test for typical electrocardiographic changes that we provoke in patients with suspected Brugada syndrome [12]. Ventricular arrhythmia might result from this test. Therefore, sodium depletion may predispose to ventricular arrhythmias. It is more difficult to find an association with the increased susceptibility to ventricular arrhythmias in patients with serum sodium concentration within the upper range area. It should be remembered that heart failure patients are usually treated with diuretics, which decrease the serum sodium concentration. Therefore, sodium concentration within the upper range area may be abnormal. Yost et al. have reported lately that sodium concentration higher than 135 mEq/L in patients implanted with extracorporeal mechanical circulatory support devices is predictive of worsened postoperative survival [13]. U-shaped association of serum sodium concentration with mortality is a well-known phenomenon [14]. Further studies are needed to assess its importance in ventricular arrhythmia occurrence in ICD patients.

Relationship between serum potassium concentration and occurrence of discharges may be very complex. On the one hand, low potassium concentration favours cardiac arrhythmias, on the other hand, numerous discharges and

de facto short aborted cardiac arrests may promote metabolic acidosis and hyperkalaemia. Low serum potassium concentration may promote both atrial fibrillation and ventricular arrhythmias, which may increase the risk of discharges that are inadequate and adequate, respectively. Complex relationship between appropriateness of ICD shocks and serum potassium concentration may result in lack of its predictive value in multivariate analysis (Tab. 2).

The finding that higher number of shocks is related with their inappropriate character are very well known phenomenon. The inappropriate discharges rarely occur as a single episode and often appear in clusters e.g. in pseudostorm [15].

The predictors of appropriate and inappropriate shocks may be different in different patients' populations [16]. Moreover the number of appropriate shocks may be modified by the modern programming of the ICD [17]. Therefore, the predictors of appropriate shocks may be different when different programming was used.

LIMITATIONS

The main limitation of the study is its retrospective character. The data may be incomplete. The data regarding current treatment were not available in a significant percentage of patients and therefore could not be included in the analysis.

CONCLUSIONS

1. Age, number of shocks, serum sodium concentration, and type of sudden cardiac death prevention are simple clinical and laboratory findings that can predict the appropriateness of ICD shocks.
2. Further studies are needed to find associations between serum sodium concentration and inappropriate shock occurrence.

REFERENCES

1. Moss AJ, Zareba W, Hall WJ et al. Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877-883.
2. Jagielski D, Zyśko D, Josiak K et al. Pacjent z interwencją wszczepialnego kardiowertera-defibrylatora w szpitalnym oddziale ratunkowym. Wiad Lek. 2018;9:1685-1689.
3. Daubert JP, Zareba W, Cannom DS et al. MADIT II Investigators. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. J Am Coll Cardiol. 2008;51(14):1357-1365.
4. Clementy N, Pierre B, Simeon E et al. Programming implantable cardioverter-defibrillators in primary prevention: higher or later. Arch Cardiovasc Dis. 2014;107(5):308-318.
5. Moss AJ, Schuger C, Beck CA et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med. 2012;367:2275-2283.
6. Jagielski D, Zyśko D, Niewiński P et al. Clinically overt infections and markers of inflammation in patients admitted to Emergency Department due to high-energy discharges of implantable cardioverter-defibrillator. Post N Med. 2018;31(6):349-352.
7. Olde Nordkamp LR, Postema PG, Knops RE et al. Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications. Heart Rhythm. 2016;13(2):443-454.
8. Rajamani K, Goldberg AS, Wilkoff BL. Shock avoidance and the newer tachycardia therapy algorithms. Cardiol Clin. 2014;32(2):191-200.
9. Sweeney MO, Wathen MS, Volosin K et al. Appropriate and inappropriate ventricular therapies, quality of life, and mortality among primary and secondary prevention implantable cardioverter defibrillator patients: results from the Pacing Fast VT REduces Shock ThErapies (PainFREE Rx II) trial. Circulation. 2005;111(22):2898-2905.
10. Kulkarni N, Link MS. Causes and Prevention of Inappropriate Implantable Cardioverter-Defibrillator Shocks. Card Electrophysiol Clin. 2018;10(1):67-74.
11. Auricchio A, Schloss EJ, Kurita T, et al. PainFree SST Investigators. Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms: PainFree SST trial primary results. Heart Rhythm. 2015;12(5):926-936.
12. Pappone C, Santinelli V. Brugada Syndrome: Progress in Diagnosis and Management. Arrhythm Electrophysiol Rev. 2019;8(1):13-18.
13. Yost G, Tatooles A, Bhat G. The Sodium Paradox: Dysnatremia and Mortality in Patients Implanted With Extracorporeal Mechanical Circulatory Support Devices. J Intensive Care Med. 2018;33(3):203-208.
14. Deubner N, Berliner D, Frey A et al. Dysnatraemia in heart failure. Eur J Heart Fail. 2012;14(10):1147-1154.
15. Georgi C, Neuß M, Möller V, Seifert M, Butter C. 105 Inappropriate ICD Shocks in a Patient with Dilated Cardiomyopathy and Broca's Aphasia. Case Rep Cardiol. 2019 Feb 14;2019:8302591.
16. Zienciuk-Krajka A, Sterliński M, Filipecki A et al. Implantable cardioverter-defibrillators in patients with long QT syndrome: a multicentre study. Kardiol Pol. 2018;76(12):1687-1696.
17. Wilkoff BL, Fauchier L, Stiles MK et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Europace. 2016;18:159–183.

Conflict of interest:
All authors declare no conflict of interest

CORRESPONDING AUTHOR

Dariusz Jagielski
Department of Cardiology, Centre for Heart Diseases,
4th Military Hospital,
ul. Weigla 5, 50-981, Wroclaw, Poland
tel: +48 261 660 237,
e-mail: dariuszjagielski@gmail.com

Received: 20.03.2019
Accepted: 28.04.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

COMPARATIVE ASSESSMENT OF BILE DUCT DECOMPRESSION METHODS IN PATIENTS WITH OBSTRUCTIVE JAUNDICE OF NON-TUMOR GENESIS

Oleg Y. Kanikovskyi, Yaroslav V. Karyi, Yura V. Babiichuk, Yevhen V. Shaprynskyi
NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSYA, UKRAINE

ABSTRACT

Introduction: Obstructive jaundice is one of the most common diseases of the digestive system observed in 10-15% of the world's population. The question of making a choice among methods of bile duct decompression is still under discussion, since both single-stage and two-stage methods of biliary decompression lead to progression of hepatic insufficiency after restoration of bile passage.

The aim: To determine a tempo of biliary decompression after external and internal drainage of bile ducts, endoscopic transpapillary interventions in patients with obstructive jaundice of non-tumor genesis.

Materials and methods: We analyzed the outcomes of surgical treatment of 180 patients with obstructive jaundice of the non-tumor genesis. The patients were divided into three groups: group I (n = 86), where endoscopic methods of biliary decompression were used; group II (n = 48), where biliodigestive anastomoses were formed; and group III (n = 46), where the external drainage of bile ducts was conducted. The average age was 62 ± 6.0 years. The average duration of obstructive jaundice was 20 ± 3.7 days.

Results: The patients of the group I demonstrated a gradual decrease of bilirubin and alkaline phosphatase levels, which reached the normal readings on Day 7. The patients of the group II demonstrated normal levels of bilirubin and alkaline phosphatase on Day 14. The patients of the group III demonstrated rapid decrease of bilirubin and alkaline phosphatase levels, which reached the normal readings on Day 28. The transaminase level in each group of patients had reached the norm earlier.

Conclusions: No significant disturbances of the functional state of the liver after endoscopic transpapillary interventions were observed. Formation of areflux biliodigestive anastomoses was accompanied by a moderate rate of biliary duct decompression. The external drainage of biliary ducts was characterized by a rapid rate of biliary decompression, leading to a post-compression syndrome.

KEY WORDS: obstructive jaundice, external drainage of biliary ducts, biliodigestive anastomosis, endoscopic transpapillary intervention

Wiad Lek 2019, 72, 7, 1247-1252

INTRODUCTION

According to WHO, obstructive jaundice (OJ) is one of the most common diseases of the digestive system observed in 10-15% of the world's population [1, 2]. The benign genesis of OJ is preconditioned by choledocholithiasis, stenotic papillitis, chronic fibrous pancreatitis, strictures of the bile ducts, parapapillary diverticula, and other diseases. The obstruction of the distal portion of the common bile duct (CBD) makes up to 14.7-35.5% of the total bile duct diseases [3, 4]. The discussion regarding a choice among the methods of biliary decompression is still underway. Most clinical institutions prefer a two-stage treatment method. Perhaps, a single-stage treatment approach is being increasingly used as the experience is gained and surgical techniques are improved [5, 6]. However, both single-stage and two-stage methods of bile duct decompression lead to a progression of hepatic insufficiency after bile duct restoration with 7-42% of patients having a fatal outcome [7, 8].

THE AIM

To determine a tempo of biliary decompression after external and internal drainage of bile ducts, endoscopic transpapillary interventions in patients with obstructive jaundice of non-tumor genesis.

MATERIALS AND METHODS

In the period from 2002 to 2018 180 patients with obstructive jaundice of non-tumor genesis received treatment at the surgical clinic of the medical faculty No. 2 of the National Pirogov Memorial Medical University 107 (59.4%) patients were females and 73 (40.6%) patients were males. The patients were divided by age according to WHO recommendations. There were 12 (6.7%) patients of a younger age, 30 (16.7%) patients of a middle age, 63 (35.0%) elderly patients, 70 (38.8%) senior patients, and 5 (2.8%) long-livers. The average age was 62 ± 6.0 years. The duration of obstructive jaundice up to 14 days was

diagnosed in 97 (53.9%) patients, from 14 to 28 days – in 60 (33.3%) patients, and more than 28 days – in 23 (12.8%) patients. The average duration of obstructive jaundice was 20 ± 3.7 days.

The obstructive jaundice underlying diseases were: choledocholithiasis – in 104 (57.8%) patients, Myrizzi`s syndrome – in 14 (7.8%) patients, common bile duct stricture – in 7 (3.9%) patients, stenotic papillitis – in 18 (10.0%) patients, chronic fibrous pancreatitis – in 10 (5.5%) patients, pancreas head cyst – in 5 (2.8%) patients, duodenal ulcer penetrated in hepatoduodenal ligament – in 2 (1.1 %) patients, and postcholecystectomy syndrome – in 20 (11.1%) individuals. Postcholecystectomy syndrome was caused by recurrent choledocholithiasis in 6 (3.3%) patients, by residual choledocholithiasis – in 8 (4.4%) patients, and by stenotic papillitis – in 6 (3.3%) patients.

Concomitant pathology was diagnosed in 156 (86.7%) patients, namely: ischemic heart disease – in 35 (19.4%) patients, hypertension – in 30 (16.7%) patients, chronic obstructive pulmonary disease – in 25 (13.9%) patients, dyscirculatory atherosclerotic encephalopathy – in 20 (11.1%) patients, diabetes mellitus – in 19 (10.6%) patients, peptic stomach and duodenal ulcer – in 14 (7.8%) patients, varicose disease of the lower extremities – in 33 (18.3%) patients, and obliterating atherosclerosis of the lower extremities vessels – in 23 (12.8%) patients. In 43 (23.9%) cases, a combination of two or more concomitant diseases was observed.

The methods of research were bioethical expertise at the Ethics and Bioethics Committee of the National Pirogov Memorial Medical University (Minutes No. 30 dated 10.12.2018). General clinical, laboratory, and instrumental study methods were used for diagnostics of bile duct obstruction. The cholestasis indicators included: an increase of the level of general and direct bilirubin, alkaline phosphatase; the indicators of the cytolytic syndrome were also assessed – a pre-surgery aspartate aminotransferase and alanine aminotransferase activity, as well as those on Days 1, 3, 5, 7, 10, 14, 28 after decompression of bile ducts.

The instrumental examination methods involved transabdominal ultrasonography, endoscopic ultrasonography, fibrogastroduodenoscopy, endoscopic retrograde pancreatic cholangiography, intraoperative cholangiography, and magnetic resonance imaging. Transabdominal ultrasonography was chosen the screening method for diagnostics of gallbladder and bile duct pathology and conducted for all patients. An echography was performed on a Lodgiq-500 PRO Series GE diagnostic unit. All patients with bile duct obstruction were subjected to fibrogastroduodenoscopy using a Pentax-290V fibrogastroduodenoscope. For direct contrast of bile ducts, endoscopic retrograde pancreatic cholangiography was performed using a 30% water-soluble contrast 10-20 ml and 3-5 ml for contrasting the main pancreatic duct. For contrasting bile ducts during surgery, intraoperative cholangiography was performed by injection of 10-20 ml of 30% contrast agent through a cystic duct remnant or a biliary duct puncture. With the impossibility of cannulation of a major duodenal papilla, endoscopic ultrasonography was applied using the Olympus Exera EU M 60 diagnostic set. The Somatom-CR computerized tomograph was used for magnetic resonance imaging of the pancreas.

RESULTS

We used transabdominal ultrasonography to detect bile duct dilatation (CBD diameter greater than 9 mm suggested the presence of bilateral hypertension) and the presence of concrements therein. At the same time, the number of concrements in CBD was precisely measured by endoscopic retrograde pancreatic cholangiography. The informativity of transabdominal ultrasonography for diagnostics of OJ causes was equal to 116 (64.4%). In 19 (10.6%) cases, the unsatisfactory results of transabdominal ultrasonography were preconditioned by severe flatulence – 7 (3.9%), obesity – 4 (2.2%), the presence of multiple small concrements (less than 3 mm) in the terminal portion of the CBD – 5 (2.8%), and aerocholia – 3 (1.7%). Endoscopic ultrasonography was used in such cases.

All patients with OJ were subjected to fibrogastroduodenoscopy, which gave the possibility to assess the shape and size of the duodenal papilla, the nature and volume of bile released, and to decide upon the possibility of further endoscopic retrograde pancreatic cholangiography. Fibrogastroduodenoscopy was also used for OJ differential diagnostics between a concrement stuck in the distal CBD and a pathology of major duodenal papilla in 18 (10.0%) patients.

Endoscopic retrograde pancreatic cholangiography was conducted in 70 (38.9%) cases. Choledocholithiasis was diagnosed in 52 (28.9%) patients, and stenotic papillitis – in 18 (10.0%) patients. Endoscopic retrograde pancreatic cholangiography failed to perform in 30 (16.7%) patients due to the presence of a calculus in the ampulla of major duodenal papilla in 19 (10.6%) patients, parapapillary diverticula in 9 (5.0%) patients, and the state after the Billroth II stomach resection in 2 (1.1%) patients. We used endoscopic ultrasonography when it was impossible to perform cannulation of major duodenal papilla. In addition, endoscopic ultrasonography made it possible to objectively estimate the proportion of calculi diameters and the terminal CBD portion. Complications after endoscopic retrograde pancreatic cholangiography were observed in 8 (4.4%) patients: acute pancreatitis – in 4 (2.2%) patients, acute cholangitis – in 2 (1.1%) patients, and bleeding from major duodenal papilla in 2 (1.1%) patients when endoscopic retrograde pancreatic cholangiography was combined with endoscopic papillosphincterotomy.

40 patients (22.2%) were subjected to intraoperative cholangiography. For that purpose, a contrast was introduced into bile ducts through a cystic duct remnant in 20 (11.1%) patients, and in 12 (6.7%) cases at puncture of CBD in patients with open cholecystectomy. During the laparoscopic cholecystectomy, intraoperative cholangiography was performed by catheterization of the cystic duct in 8 (4.4%) patients. Choledocholithiasis was diagnosed in 19 (10.6%) patients, Mirizzi`s syndrome –

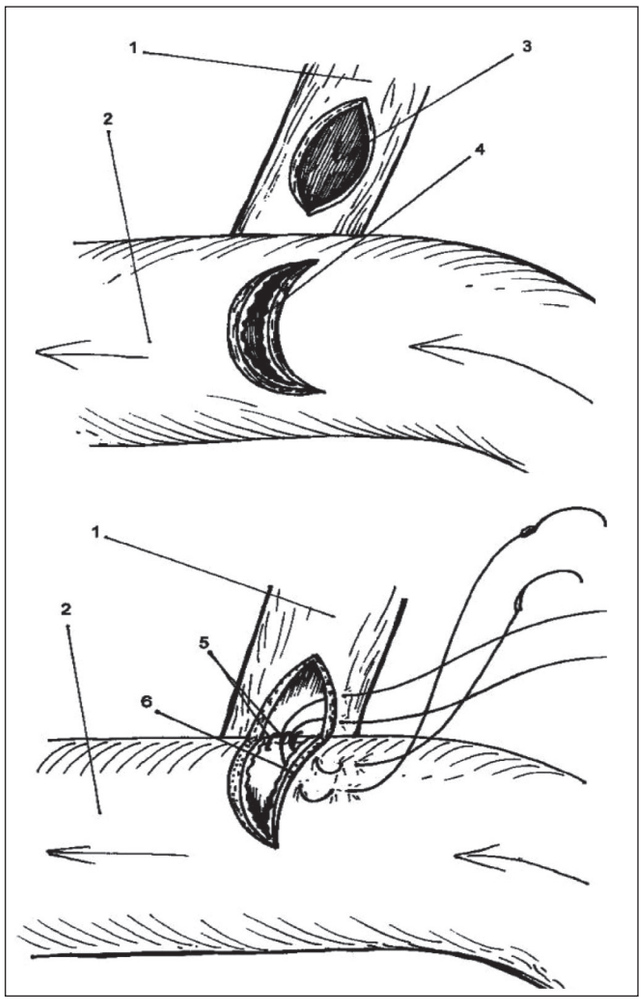


Fig. 1. A method of choledochoduodenoanastomosis formation with the use of intraoperative technique of the duodenal contents reflux prevention.

supraduodenal CBD portion – 1
descending duodenal portion – 2
longitudinal choledochotomy – 3
crescent-shaped duodenotomy – 4
choledochoduodenoanastomosis "side-to-side" – 5
duodenal opening – 6

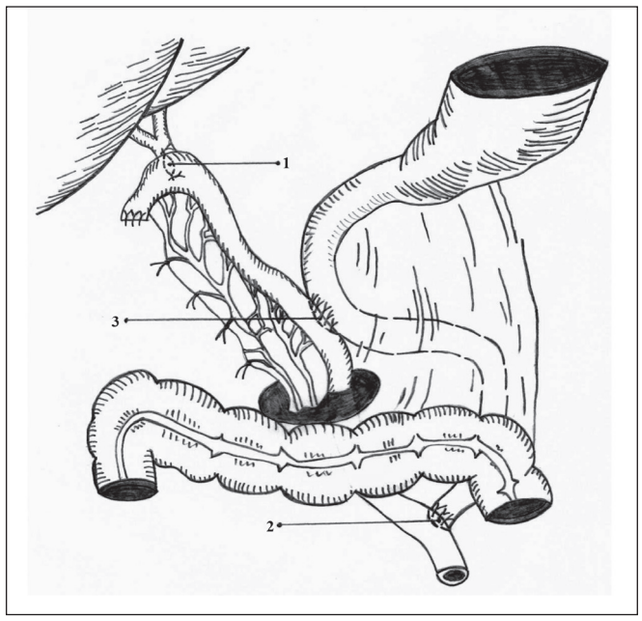


Fig. 2. A method of combined areflux hepaticojejunoduodenostomy.

hepaticojejunoanastomosis "side-to-side" – 1
interstitial anastomosis "end-to-side" – 2
duodenojejunoanastomosis "side-to-side" – 3

in 14 (7.8%) patients, and CBD stricture – in 7 (3.9%) patients. In 5 (2.8%) cases, we observed complications after introduction of contrast in the bile duct: acute pancreatitis in 3 (1.7%) patients, and acute cholangitis in 2 (1.1%) patients.

Magnetic resonance imaging was used in 17 (9.4%) patients. In case of pancreas pathology, magnetic resonance imaging was used for diagnostics of chronic fibrous pancreatitis in 10 (5.6%) patients, pancreatic head cyst – in 5 (2.8%) patients, and magnetic resonance imaging was used for diagnostics of duodenal ulcer penetrated in hepatoduodenal ligament – in 2 (1.1%) cases.

In the course of the study, the patients were divided into three groups: group I (86 patients), where endoscopic methods of biliary decompression were used, group II (48 patients), where biliodigestive anastomosis was formed, and group III (46 patients), in which external drainage of bile ducts was performed.

In group I patients, the endoscopic methods of biliary decompression were used in 86 (47.8%) cases. At the first stage, endoscopic papillary balloon dilatation was performed in 3 (1.7%) patients with single concrements up to 5 mm in diameter located in the distal CBD portions. We used balloons with a diameter of 4 and 6 mm. The balloons were filled with 30% contrast medium and monitored using rediocontrast labels. The balloon pressure was 4-9 atm. The duration of dilation was 15-60 seconds.

Incomplete endoscopic papillosphincterotomy (up to 1.0 cm) was performed in 22 (12.2%) patients with choledocholithiasis, which enabled a self-discharge of calculi with diameters up to 10 mm. In addition, we used incomplete endoscopic papillosphincterotomy in 18 (10.0%) patients with stenotic papillitis. A complete endoscopic papillosphincterotomy (over 1.0 cm) was performed in 19 (10.6%) patients, which enabled the lithoextraction using a Dormia basket (Olympus FG-22Q, Boston scientific trapezoid RX). In case of multiple calculi, we used lithoextractors with a conductor (Boston scientific trapezoid RX with guidewire PT2). After complete endoscopic papillosphincterotomy, a mechanical lithotripsy with Olympus BML-201Q lithotripter was performed in 12 (6.7%) cases of 10-20 mm calculi, followed by removal of fragmented concrements with Dormia basket.

Endobiliary transpapillar stenting (stent diameter – 7 Fr) was performed for prolonged biliary decompression in 3

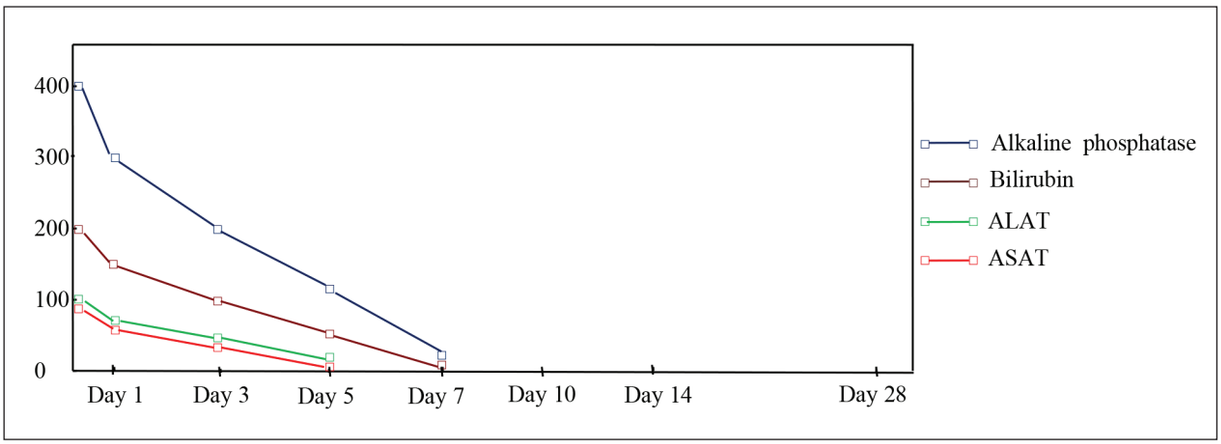


Fig. 3. Levels of bilirubin, alkaline phosphatase, ALAT, ASAT in group I patients.

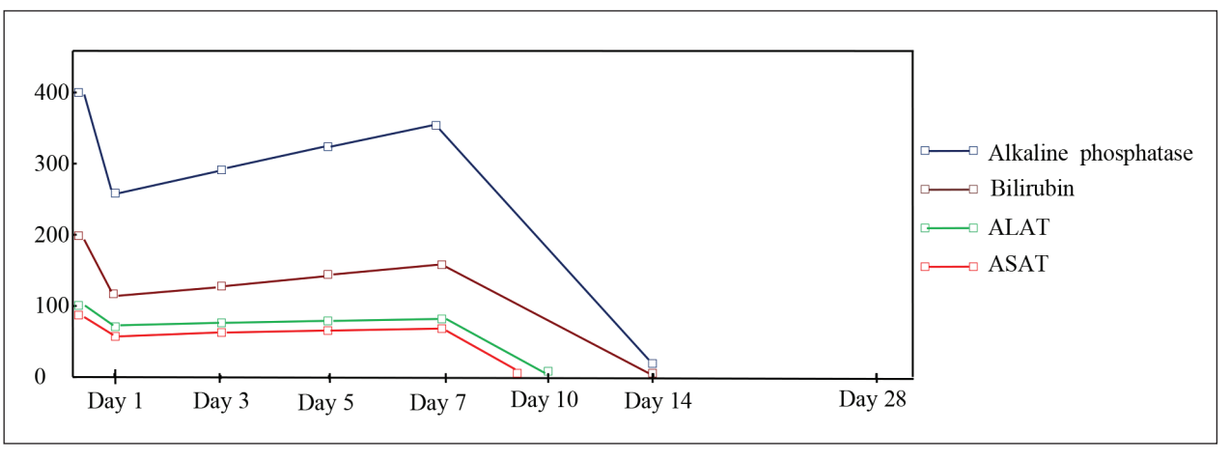


Fig. 4. Levels of bilirubin, alkaline phosphatase, ALAT, ASAT in group II patients.

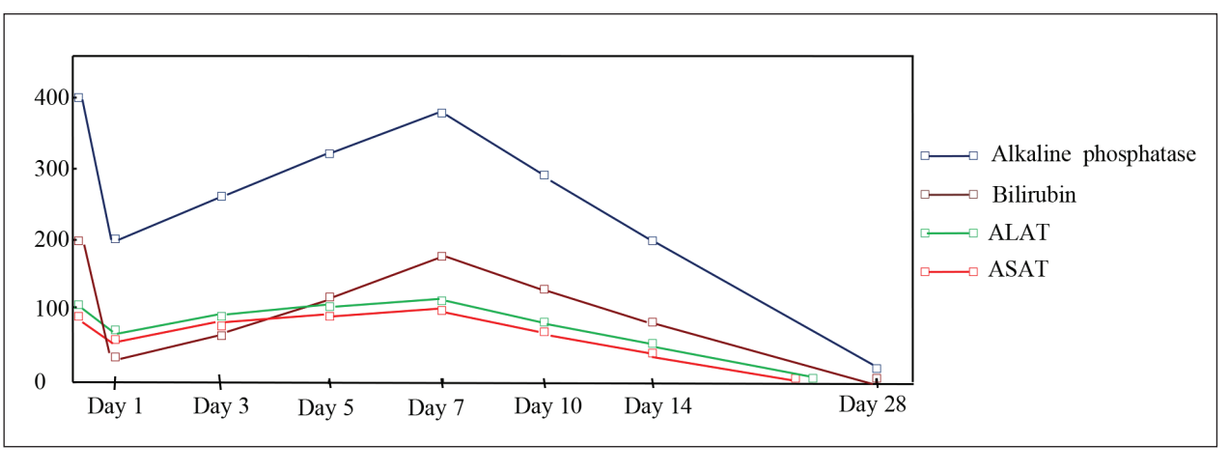


Fig. 5. Levels of bilirubin, alkaline phosphatase, ALAT, ASAT in group III patients.

(1.7%) patients with a stricture of CBD terminal portion. The stent encrusted with bile acid salts was replaced in 3-4 months. In case of purulent cholangitis, a nasobiliary drainage was performed in 9 (5.0%) patients, which made it possible to decompress and sanitation bile ducts. Laparoscopic cholecystectomy was performed at stage II, after treatment of OJ and purulent cholangitis.

Group II patients were subjected to internal drainage of bile ducts in 48 (26.7%) cases. In obstruction of distal CBD portions, a choledochoduodenoanastomosis was formed using an intraoperative technique for prevention of reflux of duodenal contents (patent of Ukraine No. 85986). We mobilized a supraduodenal CBD portion 1 and prepared a site for anastomosis on the descending duodenal portion 2. We performed a 15 mm-long longitudinal choledochotomy 3 and a crescent-shaped duodenotomy 4 in a transverse direction with a convex portion up to the intake portion of the gut. We formed a

choledochoduodenoanastomosis using a "side-to-side" technique by 5 seams in one row across all layers of the walls of both hollow organs. When forming the upper edge of the anastomosis, the seam captured the serous-muscular wall of the duodenum, retreating 10 mm from the edge of the duodenal opening 6 in the proximal direction. When tightening a knot, the crescent flap was invaginated into the duodenal cavity, forming a slit-like valve that prevented duodenobiliary reflux and rapid decompression of bile ducts after surgery (fig. 1). Areflux choledochoduodenostomy was performed in 38 (21.1%) patients: in 23 (12.8%) cases of choledocholithiasis combined with stenotic papillitis, in 10 (5.5%) cases of chronic fibrous pancreatitis, and in 5 (2.8 %) cases of the pancreas head cyst.

Combined areflux hepaticojejunoduodenostomy (patent of Ukraine No.112735) was formed in 10 (5.5%) patients, i.e. 4 (2.2%) individuals with CBD stricture and 6 (3.3%) patients with Mirizzi`s type II syndrome. The areflux hepaticojejunostomy by "side-to-side" 1 technique was performed. For that purpose, we stitched and tucked up the front wall of the empty gut to form a cone, having departed 3-4 cm from the blind end of the small intestine. Under a ligature, we dissected the intestine wall and expanded the point opening with a clamp in the transverse direction. Subsequently, we conducted a longitudinal hepaticotomy and formed an anastomosis between the common hepatic duct and the empty intestine with a 15-20 mm single-row knot suture, with adaptation of the mucous membranes of the anastomosis organs. Upon passing a peristaltic wave, the gut wall "closed", which prevented a reflux of the intestinal contents in bile duct and rapid biliary decompression. The continuity of the intestinal tube was restored by applying two-row interstitial anastomoses of the "end-to-side" 2 type, 30-40 cm from the pre-formed biliodigestive anastomosis. In order to prevent the formation of peptic ulcers and for duodenostasis prophylaxis, an additional "side-to-side" duodenojejunostomy was formed between the excluded portion of the intestine and the descending branch of the duodenum 3 (fig. 2).

Y-shaped drainage (patent of Ukraine No. 101302) was used to prevent a leakage of bile in the abdominal cavity from the line of formed biliodigestive anastomosis. The drainage tube was led out to the anterior abdominal wall through a contraincision and connected to a constant suction unit (5-10 cm of water column). Using a vacuum unit made it possible to prevent a leakage of bile into the abdominal cavity.

We performed the external drainage of bile ducts in 46 (25.5%) group III patients. Laparoscopic cholecystectomy with cysticolitotomy with a Fogarty occlusion catheter was performed in 10 (5.5%) patients with up to 5 mm concrements below the point where the cystic duct run into the common hepatic duct. Laparoscopic cholecystectomy with external drainage of CBD was performed in 8 (4.4%) patients with Mirizzi`s type I syndrome.

Open cholecystectomy with choledocholithotomy was performed in 26 (14.4%) patients with over 20 mm concrements that could not be removed transpapillary. In 20 (11.1%) patients, a probe-obturator of extrahepatic bile duct was used (patent of Ukraine No. 104826). In the postoperative period, the volume of the obturator balloon was gradually reduced for 7-10 days, which made it possible to carry out dose-controlled decompression of bile ducts and to prevent a post-decompression liver dysfunction. A separation of ulcer defect was performed in 2 (1.1%) patients with duodenal ulcer penetrated in hepatoduodenal ligament. After the separation, a 1/3 duct circle-long defect was formed in the CBD. T-shaped drainage-balloon (patent of Ukraine No.104469) was used to prevent the formation of a CBD stricture after the duct defect suturation. The balloon dilatation at the level of CBD plastics lasted 3 months. No CBD stricture signs were present after two years after the surgery.

DISCUSSION

In patients with OJ in the postoperative period, there are three syndromes: mesenchymal-inflammatory, cholestatic and cytolytic. High activity of hepatic cytolysis on the background of OJ and is a causes progression of hepatic insufficiency after bile duct restoration in the postoperative period [9, 10]. The severity of the patient's condition and the high frequency of postoperative complications have long led surgeons to the idea of multi-stage surgery in OJ [11]. Therefore, the study a tempo of the biliary decompression after various methods drainage of bile ducts will enable to prevent post-decompression liver dysfunction [12].

Gradual decrease of bilirubin and alkaline phosphatase levels on Days 1, 3, and 5 after endoscopic interventions, and reaching the normal level on Day 7 was observed in group I patients. Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) decreased to the standard levels on Day 5 (fig. 3). No significant violations of the functional state of the liver were observed after endoscopic transpapillary interventions, which is optimal for a post-compression period.

The group II patients demonstrated a decrease of bilirubin and alkaline phosphatase levels on Day 1 after formation of biliodigestive anastomoses, gradual increasing of the levels on Days 3, 5, and 7, and normalization thereof on Day 14. The ALAT activity restored on Day 10, ASAT – a day earlier (fig. 4). The formation of areflux choledochoduodeno-anastomosis and combined areflux hepaticojejunoduodenostomy was accompanied by a moderate rate of decompression of bile ducts due to the presence of a valve mechanism.

The group III patients demonstrated a rapid decrease of bilirubin and alkaline phosphatase levels on Day 1 after external drainage of bile ducts, their gradual increase on Days 3, 5, and 7, a decrease on Days 10, 14, and normalization on Day 28. The level of transaminases (ALAT, ASAT) reached the norm earlier – on Days 23 and 21, respectively (fig. 5). The external decompression of the biliary system was accompanied by a rapid decrease of pressure in bile ducts, which led to post-decompression liver dysfunction, required a dose-controlled decompression of bile ducts for 7-10 days and appropriate medicinal correction.

CONCLUSIONS

1. No significant violations of the functional state of the liver were observed after endoscopic transpapillary interventions.
2. The formation of areflux biliodigestive anastomosis was accompanied by a moderate rate of biliary duct decompression due to the presence of a valve mechanism.
3. The external drainage of biliary ducts was characterized by a rapid rate of biliary decompression, which led to a post-decompression syndrome, and required a dose-controlled decompression of bile ducts and appropriate medicamental correction.

REFERENCES

1. Topal B., Vromman K., Aerts R. Hospital cost categories of one-stage versus two-stage management of common bile duct stones. Surg. Endosc. 2010; 24: 413-416.
2. De Palma G.D., Luglio G., Maione F. et al. Endoscopic snare papillectomy: a single institutional experience of a standardized technique. A retrospective cohort study. Int. J. Surg. 2015; 13: 180-183.
3. Li Zhe-Fu, Chen Xiao-Ping. Recurrent lithiasis after surgical treatment of elderly patients with choledocholithiasis. Hepatobil. Pancr. Dis. Int. 2007; 6: 67-71.
4. Savolyuk S.I., Losyev V.O. Assessment of the structural-functional changes of the collagen in the wall of the common bile duct in acute cholangitis in patients with choledocholithiasis. Reports of morpholog. 2016; 1(22): 145-148.
5. Stark A., Hines O.J. Endoscopic and operative palliation strategies for pancreatic ductal adenocarcinoma. Semin. Oncol. 2015; 42(1): 163-176.
6. Santo, M.A., Domene C.E., Riccioppo, D. Common bile duct stones: analysis of the videolaparoscopis surgical treatment. Arg. Gastroenterol. 2012; 49(1): 41-51.
7. Desiaterik V.I., Kotov A.V., Mamchur D.V. Ways to improve the results of surgical treatment for obstructive jaundice on the background of gallstone disease. Ukrain. J. Surg. 2017; 1(32): 100-105.
8. Yang M.J., Kim J.H., Yoo B.M. et al. Partially covered versus uncovered self-expandable nitinol stents with anti-migration properties for the palliation of malignant distal biliary obstruction: A randomized controlled trial. Scand. J. Gastroenterol. 2015; 50(12): 1490-1499.
9. Orel Y.M., Dziubanovskyi O.I., Shkrobot L.V. Structural changes of liver tissue in the conditions of modelled cholestasis and after it liquidation. Hospital Surg. 2016; 2: 45-49.
10. Lilly M.C., Arregai M.E. Balanced approach to choledocholithiasis. Surg. Endoscop. 2001; 15(5): 467-472.
11. Costi R., Gnocchi A., Di Mario F. et al. Diagnosis and management of choledocholithiasis in the golden age of imaging, endoscopy and laparoscopy. World J. Gastroenterol. 2014; 20(37): 1388-1401.
12. Nychytaylo M.Y., Dziubanovskyi O.I. Comparison of dynamics of cytolytic and cholestatic indicators and the tempo of the biliary decompression after one-step laparoscopic and open operation interventions of patients with choledocholithiasis complicated with obstructive jaundice. Hospital Surg. 2017; 1: 8-16.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Yaroslav V. Karyi
Surgery Department of the Medical Faculty No.2,
National Pirogov Memorial Medical University
56 Pirogov Str., Vinnytsya 21018, Ukraine
tel: +380677429457
e-mail: yaroslavkaryi@gmail.com

Received: 10.02.2019
Accepted: 06.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

THE ASSOCIATION OF *APA*I-POLYMORPHISM OF VITAMIN D RECEPTOR GENE *(VDR)* WITH DEVELOPMENT OF GENERALIZED PARODONTITIS IN UKRAINIAN POPULATION

Ilia G. Fomenko, Viktoriia Yu. Harbuzova, Olha A. Obukhova, Vladislav V. Pohmura, Inna A. Plakhtiienko, Svitlana N. Piven
SUMY STATE UNIVERSITY, SUMY, UKRAINE

ABSTRACT

Introduction: At present, it is believed that the genetic component is important in the pathogenesis of periodontitis. One of the candidate genes that are of major importance in the development of the disease is the vitamin D receptor gene (VDR). The association of its genetic polymorphisms, in particular *Apa*I, with periodontitis in different populations of the world is proved.

The aim: To study the association of the *Apa*I-polymorphism *VDR* gene with the development of generalized periodontitis in the Ukrainian population.

Materials and methods: Patient genotypes were determined by polymerase chain reaction with subsequent analysis of restriction fragment length (PCR-RFLP) from buccal epithelium 116 patients with generalized periodontitis (GP) and 67 individuals of control group. Statistical analysis was performed by using SPSS-17,0 program.

Results: As a result of the performed studies, it was shown that in the group of patients with GP, the ratio of homozygous for the main allele (a/a), heterozygote (a/A) and homozygote for the minor allele (A/A) was 26 (22,4%), 62 (53,4%), 28 (24,2%), and in control group – 25 (37,3%), 27 (40,3%), 15 (22,4%), respectively. The distribution of genotypes in the comparison groups was not statistically significant (P = 0,084). By the method of binary logistic regression in the framework of the additive inheritance model (a/A vs a/a), a reliable relationship of the genotype with the *Apa*I-polymorphism of the *VDR* gene was established with the development of generalized periodontitis (P=0,029). It was shown that in heterozygotes (a/A) the risk of GP in 2,208 (95% CI = 1,084-4,496) times is higher than in homozygotes of the main allele (a/a). After adjusting for age, sex, smoking habit, BMI, the reliability of these results was maintained (P = 0,030).

Conclusions: The *Apa*I-polymorphism of the *VDR* gene is associated with the development of generalized periodontitis in the Ukrainian population.

KEY WORDS: generalized periodontitis, gene polymorphism, *Apa*I, *VDR*

Wiad Lek 2019, 72, 7, 1253-1257

INTRODUCTION

Periodontal diseases are the main cause of the loss of teeth among adults. It is known that intact periodontium is detected only in 12% of people; others have damaging of various degrees of severity - from initial inflammatory processes to severe destructive changes with the loss of teeth [1]. Today, cases of aggressive current of periodontitis with the progression of resorption of bone tissue of the jawbones at younger ages are becoming more frequent [2]. At present, reliable markers for assessing the predisposition of patients to the onset of periodontitis and its prognosis are not yet found, which makes it difficult to conduct timely preventive measures, early diagnosis of the disease, and the use of individual approaches in treatment. Thus, the most relevant today is the search for methods of diagnosis of periodontal diseases prior to the appearance of its clinical signs. This will avoid the development of complications of the disease, its transition to a more severe form. Moreover, modern molecular genetic methods can become irreplaceable in this matter. An important place among them is the study of the role of single nucleotide polymorphisms of candidate genes in the development of dental diseases.

Since the condition of the dento-facial system is inextricably linked to the general status of bone tissue in the body, recent studies have been conducted on the study of the polymorphism of the genes involved in the regulation of calcium homeostasis. In a number of studies, the relationship between different diseases with a disorder of metabolism of the bone tissue of the body and the pathology of periodontal disease has been demonstrated. Thus, if patients have severe bone mineral density loss, the risk of developing severe forms of generalized periodontitis increases [3], and a decrease in the density of bone tissue in the peripheral skeleton is accompanied by the loss of mineral bone density in the jaws [4].

Among the genes which polymorphisms are associated with changes in the bone tissue, a promising marker today is the vitamin D receptor gene (VDR), which has an effect on the development of periodontitis through the action on calcium metabolism, on the one hand, and the immune system on the other [5].

Many studies established the association of the polymorphisms of the VDR gene, including *Apa*I, with diseases such as osteoporosis, urolithiasis, renal osteodystrophy, various neoplasms, cardiovascular diseases, and peri-

odontal diseases [6-11]. The literature on this issue is quite heterogeneous and contradictory, which may be due to the genetic heterogeneity of the samples, as well as to various comparison parameters.

THE AIM

The purpose of this research was to study the association of *Apa*I-polymorphism of the VDR gene with the development of periodontitis among the Ukrainian population.

MATERIALS AND METHODS

The study used buccal epithelium of 116 patients with generalized periodontitis and 67 people without GP. The examination of each patient began with the collection of a common anamnesis (age, gender, body weight index (BWI), bad habits, physical activity, the main and possible risk factors for destructive periodontal disease). A special anamnesis included the information about the availability or absence of complaints of pain, teeth loosening, bleeding of gums, and bad breath. A periodontological examination of patients included instrumental and hardware methods. The clinical attachment loss (CAL), the recession of the gums, and the depth of the periodontal pocket were determined with the help of the periodontal broach. Based on these data, the patients were divided into two groups, the control group and the main one. The main group was made up of the patients with generalized periodontitis of a chronic course. Depending on the degree of severity, the main group was divided into 3 subgroups according to the clinical attachment loss: mild case - 1-2 mm CAL, average - 3-4 mm CAL, severe - more than 5 mm of CAL (American Academy of Periodontology (recommended by the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions). The panoramic X-ray images were characterized by the complete destruction of the bone tissue, based on which the severity of the disease was confirmed.

The work was performed in accordance with the principles of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with the participation of a person as a research object" and approved by the Bioethics Commission of the Medical Institute of Sumy State University. Before entering the study, all the participants provided written informed consent for the use of biological material in genetic research.

For genotyping, the buccal epithelium of the patients was collected with a special broach from the inner surface of the cheeks. The broaches were placed in 1.5 ml Eppendor tubes and stored at -20 ° C. DNA from the buccal epithelium was isolated using the NeoPrep50 DNA Magnet commercial kit ("NEOGEN", Ukraine) according to the producer's protocol.

A gene region that contained the *Apa*I site was amplified using a pair of specific primers: forward 5'-CAGAGCATGGACAGGGAGCAA-3' and reverse 5'-CACTTCGAGCACAAGGGGCGTTAGC-3' (Metabion, Germany). The amplification mixture consisted of 50-100 ng DNA, 5 μl 5x PCR buffer, 1.5mmol magnesium sulfate, 150 μm mixture of four nucleotide triphosphates, 15 pM each of the primers and 0.75 ED Taq-polymerase (Thermo Scientific, USA). The volume of the mixture was adjusted to 25 μl with deionized water. Polymerase chain reaction (PCR) was performed in the GeneAmp PCR System 2700 thermocycler (Applied Biosystems, USA). The amplification consisted of 35 cycles: 1 cycle 94 ° C (4 min), 2 to 34 cycle denaturation - 94 ° C (50 s), primer hybridization - 64.5 ° C (45 s) and elongation - 72 ° C (1 min), 35 cycle - 72 ° C (5 min). Then, 6 μl of the amplification product was incubated at 37 ° C for 20 hours with 5 ED restriction enzymes of *Apa*I (Thermo Scientific, USA) in buffer B of the following composition: 10 mM Tris-HCl (pH 7.5), 10 mM magnesium chloride, and 0.1 mg / ml of albumin. If the VDR gene at position 59979 was guanine, the amplificator, which consisted of 501 base pairs, was cleaved by the restriction enzyme *Apa*I into two fragments – 284 and 217 base pairs. When the guanine was replaced with thiamine, the site of restriction for *Apa*I disappeared, and a fragment of 501 size of a base pair formed (Fig. 1).

Detection of amplificators and restriction products was performed using a 2.5-agar gel (Sigma-Aldrich, USA) horizontal electrophoresis, which contained ethidium bromide (Sigma-Aldrich, USA). Horizontal electrophoresis (0,1A; 140V) is performed for 30 minutes. Visualization of DNA after electrophoresis is carried out using the automatic video-reading system "Vi-Tran" in a transilluminator ("Biocom", Russia).

A statistical analysis was performed using the SPSS-17 program. The relevance of Harry-Weinberg equilibrium genotype distribution was checked using the Online Encyclopedia for Genetic Epidemiology Studies (http://www.oege.org/software/hwe-mr-calc.shtml). To determine the validity of the difference between the two samples was performed using the student's t-criterion. To compare the distribution of genotypes in the study and control groups, the Pearson χ^2 criterion was used. All tests were bilateral, values $P<0,05$ were considered statistically significant.

RESULTS AND DISCUSSION

As a result of genotyping the patients in the groups of comparisons with the *Apa*I-polymorphism of the VDR gene and the statistical processing of the data obtained, the frequency of the genotypes and alleles they occur among the Ukrainian population was established, and the correspondence between the distribution of the main and minor alleles of the Hardy-Weinberg equilibrium (Table I) was verified. In the group of patients with GP, the ratio of homozygotes to the main allele (a/a), heterozygote (a/A) and homozygote for the minor allele (A/A) was 26 (22,4%), 62 (53,4%) and 28 (24,2%), while in the control it was 25 (37,3%), 27 (40,3%) and 15 (22,4%) respectively, which did not have statistical significance ($P = 0,084$). The frequency of the primary (a) and minor (A) alleles was among the patients 0,491 to 0,509, and among the healthy – 0,575 to 0,425.

At the next stage of the analysis of the results, the patients of the control and the main groups were divided into subgroups,

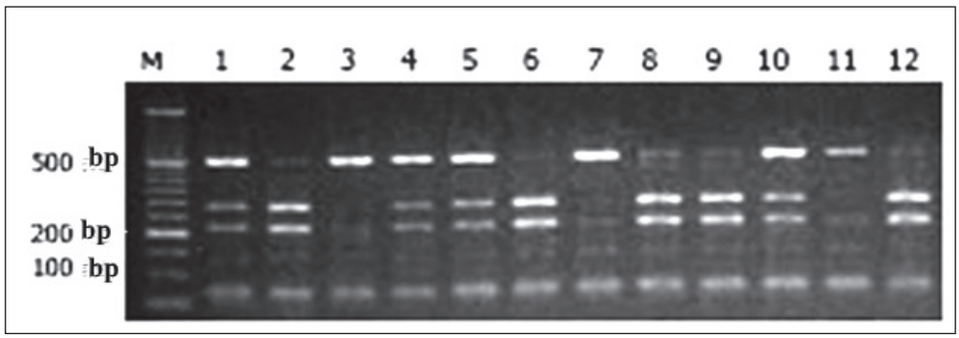


Figure 1. Results of the restriction analysis of *Apa*I-polymorphism of the VDR gene. M - molecular weight marker (in pairs of nucleic bases) of the paths 3,7,11 correspond to the genotype a/a, 1,4,5,10 - genotype a/A, 2,6,8,9,12 genotype A/A.

Table I. Distribution of alleles and genotypes by *Apa*I-polymorphism of the VDR gene in comparison groups

Genotype	Generalized periodontitis (n = 116)		Control (n = 67)		P_{HWE}	P
	n	%	n	%		
Homozygotes a/a	26	22,4	25	37,3		
Heterozygotes a/A	62	53,4	27	40,3		0.084
Homozygotes A/A	28	24,2	15	22,4		
Allele						
a	114	49,1	77	57,5	0.15	0.125
A	118	50,9	57	42,5		

Note. n - the number of patients.

Table II. Distribution of genotypes by *Apa*I-polymorphism of the VDR gene in patients with various risk factors for generalized periodontitis (GP)

Genotype	Gender			
	Female		Male	
	GP (–)	GP (+)	GP (–)	GP (+)
a/a, n (%)	13 (34,2)	12 (20,3)	12 (41,4)	14 (24,6)
a/A, n (%)	17 (44,7)	34 (57,6)	10 (34,5)	28 (49,1)
A/A, n (%)	8 (21,1)	13 (22,1)	7 (24,1)	15 (26,3)
	P = 0,291		P = 0,251	
Genotype	**Smoking**			
	Do not smoke		Smoke	
	GP (–)	GP (+)	GP (–)	GP (+)
a/a, n (%)	16 (38,1)	13 (19,7)	9 (36,0)	13 (26,0)
a/A, n (%)	18 (42,9)	38 (57,6)	9 (36,0)	24 (48,0)
A/A, n (%)	8 (19,0)	15 (22,7)	7 (28,0)	13 (26,0)
	P = 0,107		P = 0,566	
Genotype	**Body weight index (BWI)**			
	BWI < 25		BWI ≥ 25	
	GP (–)	GP (+)	GP (–)	GP (+)
a/a, n (%)	16 (34,0)	15 (27,3)	9 (45,0)	11 (18,1)
a/A, n (%)	20 (42,6)	28 (50,9)	7 (35,0)	34 (55,7)
A/A, n (%)	11 (23,4)	12 (21,8)	4 (20,0)	16 (26,2)
	P = 0,675		P = 0,051	

Note. n - the number of patients

Table III. Distribution of genotypes by *Apa*l-polymorphism of the VDR gene in the groups of patients with generalized periodontitis (GP) of various degrees of severity.

Genotype			Degree of severity GP		
			1	2	3
Homozygotes	a/a	n	10	13	3
		%	22.2	22.8	21.4
Heterozygotes	a/A	n	22	34	6
		%	48.9	59.6	42.9
Homozygotes	A/A	n	13	10	5
		%	28.9	17.6	35.7
			P = 0,539		

Note. n - the number of patients

Table IV. Analysis of association of genotypes on *Apa*l-polymorphism of the VDR gene with the risk of development of generalized periodontitis

Model	P_n	OR_n (95% CI)	P_a	OR_a (95% CI)
Dominant	0,032	2,060 (1,065–3,986)	0,036	2,088 (1,048–4,158)
Recessive	0,788	1,103 (0,540–2,254)	0,873	1,062 (0,506–2,230)
Superdominant	0,088	1,701 (0,925–3,129)	0,078	1,771 (0,938–3,347)
Additivea	0,029	2,208 (1,084–4,496)	0,030	2,279 (1,084–4,793)
	0,169	1,795 (0,780–4,131)	0,202	1,758 (0,739–4,181)

Note. 95% CI - 95% confidence interval; P_n - the observed value of P (without correction for covariates); OR_n - observed ratio of odds; P_a - the value of P after adjusting for age, gender, body mass index, obesity, the presence of arterial hypertension and the habit of smoking; ORa - odds ratio after correction for covariates; a - the first row in the additive model represents the comparison between the A/a - and a/a-genotypes, the second row is between the A/A- and a/a-genotypes.

according to sex, smoking habit, and body weight index (Table II). There were no differences in the distribution of genotypes in the group with GP and the control among people of different genders; those who smoke and do not smoke have BWI less than 25 kg / m2. However, in the subgroup of the patients with BWI more than 25 kg / m^2, the ratio of the genotypes a/a, a/A and A/A significantly differed from 11 (18,0%), 34 (55,7%) and 16 (26,3%) for the main group and 9 (45,0%), 7 (35,0%) and 4 (20,0%) for control (P = 0,051). Analysis in the subgroups of the patients with generalized periodontitis of various degrees of severity also did not reveal differences in the distribution of genotypes (Table III).

The results of the regression analysis of the association of genotypes on *Apa*I-polymorphism of the VDR gene with the development of GP in the framework of different patterns of inheritance are given in Table. IV. By the method of binary logistic regression, a statistically significant relationship was established within the additive (a/A vs a/a) model of inheritance (P_n = 0,029). The calculation of relative risk within the framework of the presented model showed that the heterozygote (a/A) had a GP risk of 2,208 (95% CI = 1,084-4,496) times higher than homozygotes to the main allele (a/a). After adjusting for age, sex, smoking habit, BWI, the reliability of these results was maintained, the P_a indicator was 0,030 (OR_a = 2,279; 95% CI = 1,084-4,793).

The VDR gene, which in humans has a length of 63,495 pairs of nucleotides, is represented by one copy and is on the 12th chromosome at position 12q13.11 [12]. The gene consists of 11 exons. Currently, 17,757 of its polymorphisms are known. *Apa*I-polymorphism is localized in the 8th intron near the 3'-UTR region (untranslated region) [13]. The polymorphic variant of *Apa*I is characterized by the replacement of guanine at position 59979 on thymine. Polymorphisms in the introns are not functionally significant, since they do not alter the sequences of nitrogenous bases in the semantic part of the gene. However, being linked to the regulatory regions of the gene, they can act as markers of the functional relationships of other SNPs with the development of pathological processes and diseases. Thus, its association with psoriasis [14], vitiligo [15], asthma [16], osteopenia [17], oncological [18], cardiovascular [10], and other diseases have been proven.

Our study has shown that *Apa*I-polymorphism of the VDR gene is associated with the development of generalized periodontitis among the Ukrainian population. Similar results were obtained in the work of other researchers. Inagaki K. et al. studied the distribution of genotypes on *Apal*-polymorphism of the VDR gene in a group of middle-aged men of the United States [19]. The frequency of genotypes according to this polymorphism was in the group under study: a/a – 41 (32,8%), a/A – 58 (46,4%), A/A – 26 (20,8%). These data are not statistically significantly different from the results we obtained (P = 0,51). In addition, the authors concluded that *Apa*I-polymorphism is

associated with alveolar bone loss, clinical attachment loss and the loss of teeth in older men. Naito M. et al. did not find a statistical connection between *Apa*I-polymorphism and the development of periodontitis among the Japanese [20]. Although the authors identified the connection between certain haplotypes and the development of chronic periodontitis. Data on the association of *Apa*I-polymorphism with the development of chronic periodontitis among the Taiwan population have been obtained [21].

CONCLUSIONS

*Apa*I-polymorphism of the VDR gene is associated with the development of generalized periodontitis among the Ukrainian population. In a heterozygote (a/A), the risk of developing the disease is 2,208 times higher than that of the homozygote in the main allele (a/a).

REFERENCES

1. Fuks EI, Kareva YuA, Galizina OA et al. Sovremennyie aspektyi etiologii i patogeneza zabolevaniy parodonta. Ros. Mediko-biologicheskiy vestnik imeni akd. I.P. Pavlova. 2013;3:153–160.
2. Firsova IV, Mokrova EA, Zavodovskiy BV et al. Vitamin D i ego rol v razvitii stomatologicheskih zabolevaniy (Obzornaya statya). Sovremennyie problemyi nauki i obrazovaniya. 2014;6.
3. Shvarts GYa. Vitamin D, D-gormon i alfakaltsidol: meditsinskie, molekulyarno-biologicheskie i farmakologicheskie aspektyi. Ukrainskiy revmatologicheskiy zhurnal. 2009;3(37):62-66.
4. Zhang L, Yin X, Wang J et al. Associations between VDR Gene Polymorphisms and Osteoporosis Risk and Bone Mineral Density in Postmenopausal Women: A systematic review and Meta-Analysis. Scientific reports. 2018;8:981. doi:10.1038/s41598-017-18670-7.
5. Zyablitskaya MS, Atrushkevich VG, Mkrtumyan AM. Rol polimorfizmov gena retseptora vitamina D v etiopatogeneze parodontita. Ros. stomat. zhurnal. 2012;5:53-57.
6. Zhang L, Yin X, Wang J et al. Associations between VDR Gene Polymorphisms and Osteoporosis Risk and Bone Mineral Density in Postmenopausal Women: A systematic review and Meta-Analysis. Nature. 2018;8:981. doi:10.1038/s41598-017-18670-7
7. Zhang P, Nie W, Jiang H. Effects of vitamin D receptor polymorphisms on urolithiasis risk: a meta-analysis. BMC Med Genet. 2013;14:104. doi:10.1186/1471-2350-14-104
8. Wang LY, Zhang P, Wang HF et al. Association of vitamin D receptor gene polymorphisms with end-stage renal disease and the development of high-turnover renal osteodystrophy in a Chinese population. Genetics and Molecular Research. 2016;15(2):gmr.6825. doi:10.4238/gmr.15026825.
9. Lin ZJ, Zhang XL, Yang ZS et al. Relationship between Vitamin D receptor gene polymorphism and renal cell carcinoma susceptibility. Journal of Cancer Research and Therapeutics. 2018;14(4):820-825.
10. He L, Wang M. Association of vitamin d receptor-a gene polymorphisms with coronary heart disease in Han Chinese. Int J Clin Exp Med. 2015;8(4):6224–6229.
11. Mashhadiabbas F, Neamatzadeh H, Nasiri R et al. Association of vitamin D receptor BsmI, TaqI, FokI, and ApaI polymorphisms with susceptibility of chronic periodontitis: A systematic review and meta-analysis based on 38 case–control studies. Dental Research Journal. 2018;15(3):155-165.
12. Labuda M, Fujiwara TM, Ross MV et al. Two hereditary defects related to vitamin D metabolism map to the same region of human chromosome 12q13– 14. J. Bone Miner. Res. 1992;7:1447–1453.
13. Liu SM, Koszewski N, Lupez M et al. Characterization of a response element in the 5′-flanking region of the avian (chicken) PTH gene that mediates negative regulation of gene transcription by 1,25-dihydroxyvitamin D3 and binds the vitamin D3 receptor. Mol Endocrinol. 1996;10:206–215.
14. Liu JL, Zhang SQ, Zeng HM. ApaI, BsmI, FokI and TaqI polymorphisms in the vitamin D receptor (VDR) gene and the risk of psoriasis: a meta-analysis. J Eur Acad Dermatol Venereol. 2013;27(6):739-746.
15. Li L, Wu Y, Cai YF et al. Association of ApaI and BsmI polymorphisms with vitiligo risk: a meta-analysis. Clin Exp Dermatol. 2015;40(7):794-803.
16. Iordanidou M, Paraskakis E, Giannakopoulou E et al. Vitamin D receptor ApaI a allele is associated with better childhood asthma control and improvement in ability for daily activities. OMICS. 2014:18(11):673-681.
17. Sassi R, Sahli H, Souissi C et al. Polymorphisms in VDR gene in Tunisian postmenopausal women are associated with osteopenia phenotype. Climacteric. 2015;18(4):624-630.
18. Song GG, Lee YH. Vitamin D receptor FokI, BsmI, ApaI, and TaqI polymorphisms and susceptibility to ovarian cancer: a meta-analysis. This meta-analysis suggests that the VDR FokI and ApaI polymorphisms are associated with susceptibility to ovarian cancer in European populations. Immunol Invest. 2013;42(7):661-672.
19. Inagaki K, Krall EA, Fleet JC et al. Vitamin D receptor alleles, periodontal disease progression, and tooth loss in the VA dental longitudinal study. J Periodontol. 2003;74(2):161-167.
20. Naito M, Miyaki K, Naito T. et al. Association between vitamin D receptor gene haplotypes and chronic periodontitis among Japanese men. Int J Med Sci. 2007;4(4):216–222.
21. Ho YP, Lin YC, Yang YH. et al. Association of vitamin D receptor gene polymorphisms and periodontitis in a Taiwanese Han population. Journal of Dental Sciences. 2017;12(4):360-367.

The presented work has been carried out within the framework of the topic of scientific research of the Department of Physiology and Pathophysiology with the course of medical biology of the Sumy State University Pathological significance of single nucleotide polymorphism in the development of common pathological processes and diseases of a person, state registration number 0114U006297.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Victoria Y. Garbuzova
st. Sanatorna 31/5, Sumy, Ukraine
tel: +380994841200
e-mail: v.garbuzova@med.sumdu.edu.ua

Received: 25.02.2019
Accepted: 10.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

POSSIBILITIES OF MODERN X-RAY EXAMINATION METHODS FOR DIAGNOSTICS OF HIDDEN DENTAL CARIES OF APPROXIMAL LOCALIZATION

Iryna I. Sokolova[1], Svitlana I. German[1], Tetiana V. Tomilina[1], Yuliia O. Slynko[1], Anatoliy M. Potapchuk[2], Karyna V. Skydan[1], Nataliia M. Udovychenko[1]

[1] KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE
[2] UZHHOROD NATIONAL UNIVERSITY, UZHHOROD, UKRAINE

ABSTRACT

Introduction: In case of hidden carious cavities development on the approximal teeth surfaces, the clinical diagnostics of this process is difficult. Then, the diagnostics of carious lesion is not possible without carrying out X-ray examination.

The aim of the study was a comparative analysis of the effectiveness of clinical and X-ray diagnostics for hidden caries of approximal teeth surfaces.

Materials and methods: Condition of 2 963 teeth of 115 people aged from 19 to 55 was analysed. Additionally, a digital panoramic 2D diagnostics (Planmeca ProSensor, Finland) and Cone Beam Computed Tomography 3D Diagnostics (Morita, Japan) were used for clinical examination of patients.

Results: In both variants of diagnostics, the number of caries defects in the upper jaw was higher than in the lower one, and the frequency of caries lesion of various teeth groups had the following sequence in descending order: molar teeth, premolar teeth, incisor teeth and canine teeth. Hidden carious cavities of average depth and deep were detected with almost the same frequency in both variants of the study, which by 1.9 - 2.0 times respectively exceeded the frequency of superficial carious cavities detection ($p = 0.0001$). According to the results of clinical studies, hidden superficial carious cavities occurred in single cases and X-ray examination improved their diagnostics by 9.6 times ($p = 0.0000$).

Conclusions: X-ray examination allows increasing the effectiveness of diagnostics of hidden carious cavities of approximal localization by 1.2 times on the whole ($p < 0,05$). In such cases orthopantomography (OPG) has reasonably sufficient diagnostic capabilities. Definitely, 3D Cone Beam Computed Tomography (CBCT) has much more diagnostic capabilities, but its use can not be justified for the diagnostics of caries only.

KEY WORDS: dental caries, hidden cavities, approximal localization, OPG, CBCT

Wiad Lek 2019, 72, 7, 1258-1264

INTRODUCTION

Nowadays dental caries remains the most widespread dental disease in the world, and dentists devote most of their time to its treatment. In many cases, cariosity diagnostics does not cause difficulties – caries lesion is easily recognized clinically, and, as a rule, there is no need for X-ray examination. But with caries localization on approximal surfaces, especially with teeth overcrowding, root cement caries in the subgingival area, in deep figures with a narrow inlet, in cases of suspicion of secondary caries under dental fillings or crowns, X-ray examination is crucial for diagnostics and generation of treatment planning [1, 2].

Previously, X-ray method of examination was considered additional in dentistry, in particular, in treatment of uncomplicated caries it was almost not used. But over time, due to visualization technologies progress, X-ray method of examination gradually gained a proper place among the basic diagnostic methods [3, 4, 5]. Firstly, the final diagnosis is made in view of X-ray data in the great majority of cases; secondly, no dental intervention can be considered relevant without detailed X-ray monitoring; thirdly, follow-up visits and dispensary observation of the patient should be based on regular X-ray control [5, 6, 7, 8, 9, 10].

The most up-to-date method for unbiased findings acquisition until 2007 was orthopantomography (OPG). This type of X-ray examination is widely used in dentistry today as well, but with the advent of 3D technology in radiology (Cone Beam Computed Tomography, CBCT) OPG is predominantly prescribed for the primary diagnostics [11, 12, 13].

It is known that a certain projection distortion of the object by magnitude or configuration occurs in the process of carrying out two-dimensional X-ray examination, which includes OPG [5]. It is believed that only CBCT carrying out offers the opportunity to accurately measure the distance in a straight line or a curve from one point to another, to determine the measure of the angle between the lines or areas. The object is scanned without projection

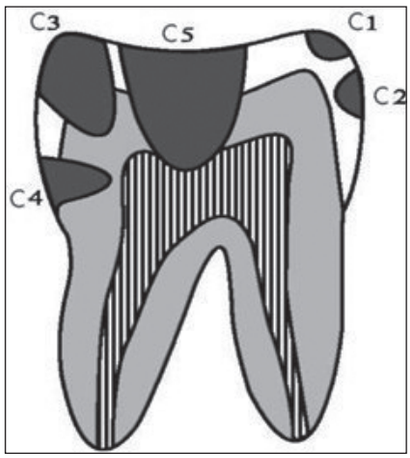


Fig. 1. X-ray classification of carious defect depth according to J. Espelid, B. Tveit (1986): C_1 – dental cavity located only within half the width of enamel; C_2 – caries that damages more than half the thickness of enamel but does not reach amelodentinal junction; C_3 – caries of enamel and dentine, in which defect takes at least half the layer of hard tooth tissues to the tooth cavity; C_4 - defect that takes more than half the thickness of dentine but is not connected to the tooth cavity; C_5 – carious defect that can reach tooth cavity.

distortion and without loss of data, practically «one to one» [2, 6, 14, 15].

Spin-Neto and co-writers (2013) [16] were interested in the problem of artifacts when the patient moved, which lead to images blurring and, consequently, to their unsuitability for diagnostic purposes. The movements of patients include breathing, heartbeats, muscle contraction and tremor. When this happens, the image becomes blurred, which is manifested in striped or annular artifacts as well as double contours. The movement of the patient leads to geometrical errors in the reconstruction process, which in turn causes poor image quality in the final format.

The authors also emphasized that the effective radiation dose for intraoral images varies from 1 to 8 microsieverts (μSv), while the effective dose when using CBCT will be higher.

Young and co-writers (2009) [17] carried out similar studies in vitro, also using 3D Accuitomo® (Morita, Japan) and compared it with solid-state sensor from Gendex® (US) in relation to caries detection. Researchers found interproximal lesions in dentine particularly with the help of CBCT images. As for interproximal enamel lesions, both CBCT and solid-state sensor showed the worst diagnostic results. But CBCT, according to the authors, more often leads to false-positive conclusions in case of caries on occlusal surfaces of teeth. It was also noted that the probability of false-positive results increased since the dentine zones display was occasionally less radiopaque. It is obvious that this false radiolucency can be caused by the geometry of irradiation, since the attenuation degree of X-rays in the dentine under the enamel tubercles is less than in the dentine of any other part of coronal part of teeth.

This effect could be avoided if it were not for separate teeth examination. An effective radiation dose of 20 μSv, which patients undergo when passing 40x40 mm CBCT scanning with Accuitomo® (Morita, Japan) is significantly differerent in comparison with four X-ray images of dental occlusion with a rectandular collimator (5 μSv).

Computer tomographic scanners are not the same, there are many modifications and not each type of a device can be effectively, and most importantly - justifiably and safely used in dentistry. Thus, in a study of a skull the patient receives 1000-1500 μSv (microsieverts) on a sequental conventional tomographic scanner, at least 400 μSv – on a spiral one and only 45-60 μSv with CBCT. We consider this advantage to be extremely important, as during X-ray studies a patient should not receive radiation exposure exceeding 1 Sv per year [7, 18].

Despite high quality of the image, the use of CBCT in dentistry has some disadvantages. Metal fillings, dental protheses, that are often in mouths of patients, cause scattered artifacts that interfere with anatomical structures identification. However, they are leveled off in the process of information processing with the artifact elimination program [3].

Tissue section on a fifth-generation dental computer tomographic scanner Vereviewepocs 3D R100 (Morita, Japan), that is used to carry out CBCT of maxillofacial area at one of the clinical bases of the Department of Dentistry of Kharkiv National Medical University, is 0.125 mm for the study of a small segment (4x4 cm) and 0.160 mm for jaws in general, which allows to diagnose minor defects.

Thus, the data accumulation regarding comparison of possible diagnostic consideration of various modern methods of X-ray diagnostics of cariosity, especially hidden caries, remains relevant today.

THE AIM

The aim of the study was carrying out a comparative analysis of clinical and X-ray diagnostics with hidden dental caries of approximal surfaces.

MATERIALS AND METHODS

115 people (68 females and 47 males at the age from 19 to 55) were involved in the study. Dental health of 2963 teeth was analyzed. The diagnostics of caries of hard tooth tissues was based on the clinical classification according to lesion depth (caries in the stain stage, superficial, medium and deep caries) and on X-Ray classification according to J. Espelid, B. Tveit (1986) (Fig. 1). Periodontal probe Explorer was used for an in-depth clinical examination, and the following equipment was used for X-ray examination: an innovative fifth-generation dental computer tomographic scanner Vereviewepocs 3D R100 (Morita, Japan) - for digital panoramic 2D diagnostics (OPG) and Cone Beam Computed Tomography (CBCT) in 3D mode; an intraoral sensor of a new standard Planmeca ProSensor (Finland) -

Table I. The number of clinically detected hidden carious cavities, depending on teeth group, localization and lesion depth, (abs., %)

Localization of carious defects, teeth group, lesion depth	The number of carious defects	
	n	%
Approximal surfaces of molar teeth	**188**	**50.81**
upper jaw:	102	54.25
of these superficial	2	
medium	45	
deep	55	
lower jaw:	86	45.75
of these superficial	-	
medium	47	
deep	39	
Approximal surfaces of premolar teeth	**119**	**32.16**
upper jaw:	61	51.26
of these superficial	-	
medium	24	
deep	37	
lower jaw:	58	48.74
of these superficial	-	
medium	21	
deep	37	
Approximal surfaces of canine teeth	**11**	**2.97**
upper jaw:	10	90.9
of these superficial	-	
medium	2	
deep	8	
lower jaw:	1	9.09
of these superficial	-	
medium	-	
deep	1	
Approximal surfaces of incisor teeth	**52**	**14.05**
upper jaw:	44	84.62
of these superficial	7	
medium	25	
deep	12	
lower jaw:	8	15.38
of these superficial	-	
medium	5	
deep	3	
Total	370	12.48

for local 2D diagnostics of several teeth in radiovisiography mode.

Caries diagnostics was carried out under the conditions of clinical encounter of patients based at University Dental Center of Kharkiv National Medical University. Certification for X-ray study carrying out normally occurred after dental examination. However, in some cases CBCT images made for other purposes such as in-depth diagnostics of endodontal pathology, periodontal diseases, sinus pathology, when planning dental implantation, etc. were evaluated first, and then clinical evaluation of teeth condition of these patients was performed.

The study conducted in accordance with the 7th revision of the principles of the Declaration of Helsinki (2013), the European Convention on Human Rights and Biomedicine.

Statistical processing of the actual material was carried out using a statistical package Statistica 13.2 with Fisher's z test and chi-square test.

RESULTS AND DISCUSSION

According to the results of the analysis of hard tissues condition of 2963 teeth, we clinically diagnosed 370 hidden carious lesions of approximal teeth surfaces, which was 12.48 ± 1.2% of cases (Table I). Carrying out X-ray examination allowed us to additionally detect 78 more hidden carious cavities of the specified localization (2.63 ± 0.2%) (Table II) and increase the effectiveness of their diagnostics by 1.2 times ($p<0,05$).

That is, the combination of both diagnostic methods allowed us to diagnose only 448 hidden caries cavities, which was 15.11 ± 1.7% of total teeth number, the condition of which was analyzed (Table II).

Table II. The number of X-ray detected hidden carious cavities depending on teeth group, localization and lesion depth, (abs., %)

Localization of carious defects, teeth group, lesion depth	The number of carious defects		The level of significance in comparison with clinically detected carious defects
	n	%	
Approximal surfaces of molar teeth	**243**	**54.25**	**0.5362**
upper jaw:	131	53.91	0.9515
of these C1	7		
C2	25		
C3	54		
C4	42		
C5	3		
lower jaw:	112	46.09	0.9620
of these C1	6		
C2	16		
C3	49		
C4	36		
C5	5		
Approximal surfaces of premolar teeth	**136**	**30.36**	**0.7569**
upper jaw:	73	53.68	0.7800
of these C1	5		
C2	8		
C3	23		
C4	36		
C5	1		
lower jaw:	63	46.32	0.7900
of these C1	1		
C2	4		
C3	21		
C4	37		
C5	-		
Approximal surfaces of canine teeth	**11**	**2.45**	**0.7838**
upper jaw:	10	90.91	0.9994
of these C1			
C2	1		
C3	2		
C4	7		
C5	-		
lower jaw:	1	9.09	-
of these C1	-		
C2	-		
C3	-		
C4	1		
C5	-		
Approximal surfaces of incisor teeth	**58**	**12.95**	**0.8660**
upper jaw:	48	82.76	0.8096
of these C1	3		
C2	8		
C3	25		
C4	12		
C5	-		
lower jaw:	10	17.24	0.9157
of these C1	-		
C2	2		
C3	5		
C4	3		
C5	-		
Total	448	15.11	0.2777

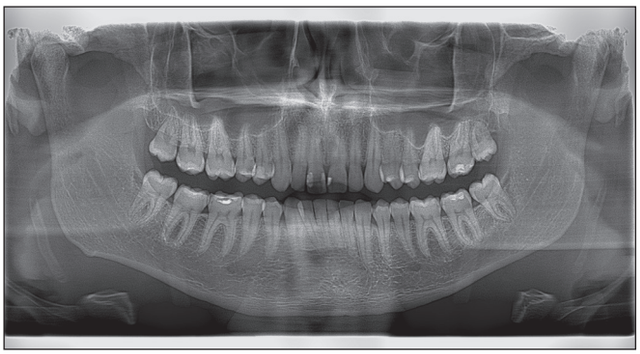


Fig. 2. Orthopantomography (OPG) of a patient D. Hidden carious cavities in teeth 1.5 (K3), 3.8 (K1), 3.7.(K1, K2), 3.6 (K2), 4.6 (K2)

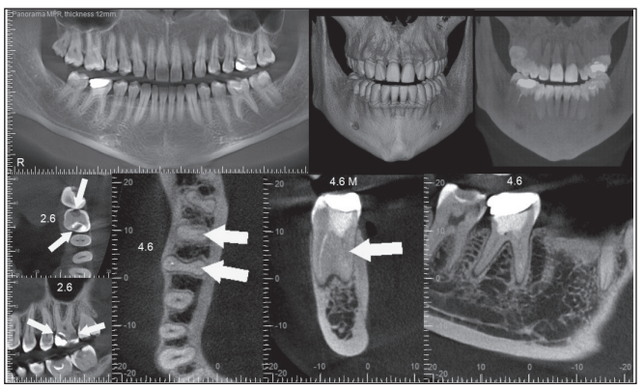


Fig. 3. OPG and CBCT screenshots of a patient P. Hidden carious cavities in teeth 2.6 (K4), 4.7 (K5)

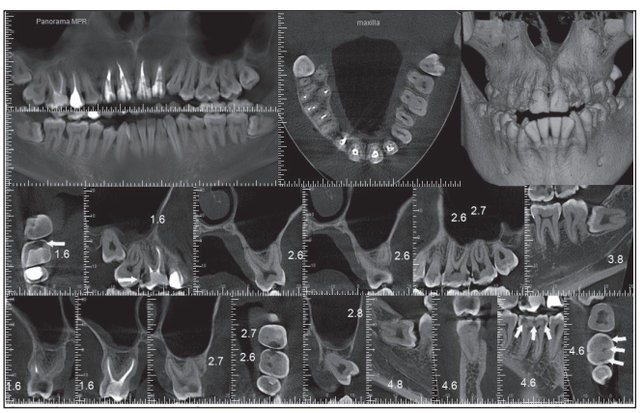


Fig. 4. OPG and CBCT screenshots of a patient H. Hidden carious cavities in teeth 2.6 (K3), 2.7 (K4), 4.6 (K2, K3), 4.8 (K1)

The data in the tables show that the frequency of hidden carious cavities detection was different depending on teeth group. It should also be noted that this dependence persisted both in clinical diagnostics and X-ray study. Thus, the number of hidden carious cavities was the highest in molar teeth (50.81% in the clinical study and 54.25% - in X-ray study, p = 0.5362). Among premolar teeth the number of hidden cavities was somewhat lower – 32.16% and 30.36% respectively, p = 0.7569. In the frontal group of teeth hidden cavities were recorded in even smaller number: among incisor teeth in 14.05% and 12.95% of cases respectively (p = 0.8660) and among canine teeth – in 2.97% and 2.45% of cases respectively (p=0,7838). That is, the frequency of caries lesion of different teeth groups had the following sequence in descending order: molar teeth, premolar teeth, incisor teeth and canine teeth, which coincides with the data of Mykhalchenko A.V. and co-writers [19].

Regarding the detection of hidden carious cavities depending on the jaws, the number of caries defects in the upper jaw was higher than in the lower jaw in both variants of the study. With that, the difference in the number of hidden cavities in upper and lower jaws was statistically significant only in frontal teeth group: in clinical study – p = 0.0001 among canine teeth and p = 0.0000 among incisor teeth; in X-ray study – p = 0.0000 among canine teeth and incisor teeth.

The characteristics of hidden carious defects according to the lesion depth was the following. Signs of carious process on approximal surfaces only within the enamel were detected clinically in 9 teeth (0.30 ± 0.1%), and using X-ray according to the criteria C1 and C2 - in 86 teeth (2.90 ± 0.1%), that is 9.6 times more (p=0,0000). The occurrence of carious cavities of medium depth was diagnosed in 169 teeth (5.70 ± 0.2%) using the clinical method and - in 179 teeth (6.04 ± 0.2%) using X-ray (according to the criterion C3). Deep carious cavities were detected clinically in 192 teeth (6.47 ± 0.3%) and using X-ray (according to the criteria C4 and C5) - in 183 teeth (6.17 ± 0.1%). That is, hidden carious cavities of medium depth as well as deep cavities were detected with almost the same frequency in both variants of the study, which by 1.9 - 2.0 times respectively exceeded the frequency of superficial carious cavities detection (p = 0.0001). Taking into account the results of clinical studies presented in Table I, superficial carious cavities are detected in single cases or are not detected at all. X-ray examination helps to improve the diagnostics of caries at early stages of its development (C1 and C2), which is confirmed by the data in Table II.

Some errors were made during the analysis of the obtained data of X-ray examination (OPG), the total number of which was 24 cases. Given that, the bulk of errors (22 observations, 91.7 ± 5.6%) was accounted for overdiagnosis. False picture of carious lesions in 22 teeth was due to dental fillings of X-ray transparent materials that do not have a geometrically correct shape and are placed without cavity liners. Overdiagnosis in remaining observations (2 cases, 8.3 ± 0.6%) is associated with the location of carious cavities below the contour height. The crucial part in clarifying the truth was to carry out in-depth X-ray examination - CBCT.

Examples of detecting hidden carious defects on OPG and in CBCT screenshots are presented in Fig. 2 - 4.

It should be noted that, in our opinion, X-ray examination was virtually irrelevant for effective diagnostics on the condition of high-quality images.

However, comparison of X-ray data with the results of clinical examination showed that distortion of carious defects sizes occurred quite often. The degree of distortions was the smallest on CBCT and OPG. The risk of false in-

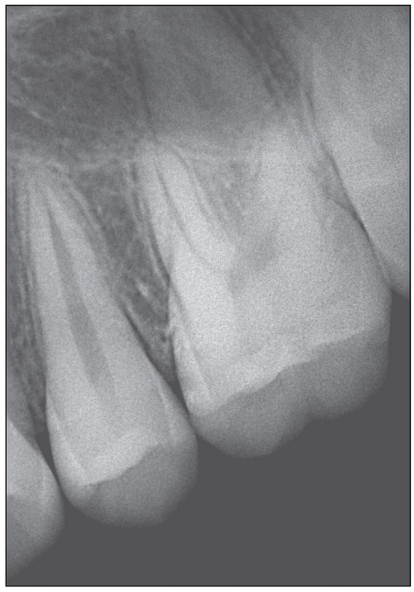


Fig. 5. Local 2D diagnostics of teeth 2.5, 2.6 in radiovisiography mode. Hidden carious cavity in a tooth 2.6 (K1)

formation was higher when carrying out OPG compared with CBCT. The reason for this in the area of incisor teeth was overlapping of the shadow from the tongue and in the area of canine teeth and premolar teeth - overlapping of approximal surfaces of adjacent teeth. The best diagnostic capabilities were in incisor teeth and molar teeth.

While carrying out CBCT, especially on the latest-generation devices, the risk of improper visualization of hidden cariosity was virtually absent and possible only in the presence of anomalies in dentition.

According to the results of the study, X-ray diagnostics of hidden caries defects among all the teeth groups was the most complicated in upper premolar teeth due to the peculiarities of the shape of these teeth and the degree of their shadows overlapping.

In case of suspicion of hidden carious cavity after carried out clinical examination, it is generally enough to refer the patient to a local 2D diagnostic procedure of several teeth in radiovisiography mode (Fig. 5).

In our opinion, it is necessary to extend the readings to X-ray examination for dental caries. The preference is to be given to orthopantomography, taking into account reasonably sufficient diagnostic capabilities of this method. Orthopantomography should be carried out strictly in the position of central occlusion in order to avoid dental tissues overlapping. In complicated cases it is rational to carry out 3D X-ray diagnostics, which allows obtaining more accurate image not only in sagital (like orthopantomography), but also in transversal and axial projections. But the use of CBCT can not be justified for the diagnostics of caries only, which coincides with the opinion of Young and others (2009), Wenzel and others (2013). The latter may, however, be an occasional finding during CBCT on condition of necessity for diagnostics of endodontal pathology, periodontal diseases in order to plan a dental implantation etc.

CONCLUSIONS

Methods of 2D diagnostics – OPG and radiovisiography have reasonably sufficient diagnostic capabilities. 3D diagnostics should never be used for caries diagnostics only. But, undoubtedly, only CBCT provides an optimal diagnostic capability to evaluate not only the topography of hidden carious cavities, but their sizes as well. Therefore, carrying out 3D diagnostics may be recommended for in-depth study of a specific clinical situation.

It would be appropriate to consider the study of frequency of secondary caries occurrence with the use of modern X-ray methods as perspectives of further researches.

REFERENCES

1. Vasil'yev A.Y. Luchevaya diagnostika v stomatologii:natsional'noye rukovodstvo. M.: GEOTAR-Media, 2010; 288.
2. Ritter I., Reiz S., Rothamel D. et al. Registration accuracy of three-dimensional surface and cone beam computed tomography data for virtual implant planning. Clin. Oral Implant. Res. 2012;XXIII,4:447-452.
3. Arkhipov A.V., Arkhipov V.D., Vyrmaskin S.I. [i dr.] Effektivnost' sovremennykh metodov rentgenologicheskogo obsledovaniya v usloviyakh stomatologicheskoy polikliniki. Izvestiya Samarskogo nauchnogo sentra Rossiyskoy akademii nauk. 2014;XVI,5(4):1364-1367.
4. Borisenko A.V. A.V.Borisenko, Pechkovskiy K.Ye., Nesin A.F. [i dr.] Rentgenologicheskaya diagnostika pul'pita. Sovremennaya stomatologiya. 2013;3:19-21.
5. Kulakov A.A. Ekspertiza kachestva okazaniya stomatologicheskoy pomoshchi (klinicheskiye aspekty). M., 2012:398.
6. Chibisova M.A., Zubareva A.A., Dudarev A.L., Shavgulidze M.A. Primeneniye konusno-luchevoy komp'yuternoy tomografii v khirurgicheskoy stomatologii, chelyustno-litsevoy khirurgii i otorinolaringologii dlya differentsial'noy diagnostiki stomatologicheskikh zabolevaniy. Stomatolog-praktik. 2012;4:20-25.
7. Fanakin V.A., Butyugin I.A., Batanova Ye.V. Konusno-luchevaya komp'yuternaya tomografiya v detskoy stomatologii: Problemy stomatologii. Actual problems of stomatology. 2014;4.
8. Aggarwal V., Logani A.. Shah N.: The evaluation of computed tomography scans and ultrasounds in the differential diagnosis of periapical lesions. J Endod. 2008; XXXIV, 11: 1312-1315.doi:10.1016/j.joen.2008.08.005.
9. Chan H.I. Mbch I.C. Wang H.L. Dental imaging in implant treatment planning. Implant Dent. 2010; 19: 288-298. doi: 10.1097/ID.0b013e3181e59ebd.
10. Henriqucs J.C, Castilho J.C., Jacobs R.. Amorim J.B., Rosa RJL, Matai GV„- Correlation between hand/wrist and panoramic radiographs in severe secondary hyperparathyroidism. Clin. Oral Invcstig. 2012; 16. doi: 10.1007/s00784-013-1025-0. Epub 2013 Jul 12.
11. Adams G.I., Gansky S.A., Miller A.I., Harrell W.E., Hatcher D.C. Comparison between traditional 2-demensional cephalometry and 3-demensional approach on human dry skulls. Am. J. Orthod. and Dentofacial Orthop. 2004; LXXIV, 4: 397-409. doi:10.1016/S0889540604003439.
12. Cartes G., Garey I., Deana N., Navarro P., Alves N. Mandibular Canal Course and the Position of the Mental Foramen by Panoramic X-Ray in Chilean Individuals. Biomed Res Int. 2018. Jun. 7; doi: 10. 1155/2018/2709401.
13. Jacobson A., Jacobson RJ-: Radiographic cephalometry. From basics to 3-D imaging. Quintessence Books. 2006. ISBN 10: 0867154616 ISBN 13: 9780867154610.
14. Rogatskin D.V. Radiodiagnostika chelyustno-litsevoy oblasti. Konusno-luchevaya komp'yuternaya tomografiya. Osnovy vizualizatsii. – L'vov: GalDent, 2010. – 148 s.

15. Ruzhilo-Kalinovskaya I., Ruzhilo T.K. Trekhmernaya tomografiya v stomatologicheskoy praktike. Per. s pol'sk. L'vov, 2012: 584.
16. Spin-Neto R., Mudrak J., Matzen L.H. et al. Cone beam CT image artefacts related to head motion simulated by a robot skull: visual characteristics and impact on image quality. Dentomaxillofac Radiol. 2013; Feb. XXXXII (2): 1-8. doi: 10.1259/dmfr/32310645.
17. Young S.M., Lee J.T., Hodges R.J. et al. A comparative study of high-resolution cone beam computed tomography and chargedcoupled device sensors for detecting caries. Dentomaxillofac Rad. 2009; 38: 445-51.
18. Batista W.O.C.. Nawarro MYT.. Maia A.F.: Effective doses in panoramic image from conventional and СВСГТ equpiment. Radial Prot Dosimetry. 2012; CLI (1): 67-75. doi:10.1148/radiol.2481071451.
19. Mikhal'chenko A.V., Mikhal'chenko D.V., Zakhvatoshina M.A., Filyuk Ye.A. Kharakternyye lokalizatsii defektov tverdykh tkaney zubov u vzroslykh. Fundamental'nyye issledovaniya. 2014; 4:114-117.

The article is prepared within the framework of the initiative research work implementation of the Department of Dentistry of Kharkiv National Medical University «Development of new methods of diagnostics, treatment and prevention of dental pathology in children and adults», the implementation period is 2015-2017, the registration code is 0115U000230 (the head is Professor I.I.Sokolova) and research work of the Department of Dentistry of post-graduate education with the course of therapeutic and orthopedic dentistry of Uzhhorod National University «Study of a problem of biological effects of iodine-fluorine deficiency in the environment on the intensity of clinical course of maxillofacial area pathology. Modern diagnostic methods and characteristics of comprehensive treatment», the implementation period is 2016-2018, the registration code is 0114U001382 (the head is Professor A.M. Potapchuk).

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Iryna I. Sokolova
Kharkiv National Medical University
Kharkiv, Ukraine
tel: +380503433988
e-mail: sokdentirina@gmail.com

Received: 11.02.2019
Accepted: 04.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

THE RELATIONSHIP OF VIP LEVEL WITH CARDIOPULMONARY PARAMETERS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN COMBINATION WITH HYPERTENSION

Valeriy A. Kapustnik, Olga V. Istomina
KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) with hypertension occupy a leading position in morbidity and mortality in the world. The question of studying a single pathological way of their development, the search for diagnostic markers and therapeutic targets in this comorbid pathology remains relevant.

The aim of the study was to study cardiopulmonary parameters in patients with chronic obstructive pulmonary disease with concomitant hypertension, depending on the level of vasoactive intestinal peptide (VIP).

Materials and methods: 99 patients with COPD GOLD 2 were examined, 54 of whom had concomitant hypertension II stage, in which the dependence of lipid metabolism, spirometry and hemodynamic parameters, depending on the level of VIP in blood serum.

Results and conclusions: It was established that the smallest values of VIP and the greatest changes in cardiopulmonary parameters, lipid metabolism were found in the cohort of persons with concomitant hypertension. There was a significant decrease in spirometry values and an increase in hemodynamic parameters, respectively, a decrease in VIP levels in patients with COPD in combination with hypertension, which may indicate its role in the formation of these pathologies due to a decrease in its protective function, both in relation to apoptosis of alveolar cells and in relation to progression atherosclerosis and high blood pressure. It was also noted that in patients with the lowest VIP serum levels, a more rapid formation of COPD was observed. The data obtained make it possible to consider VIP as a diagnostic marker and a potential therapeutic target for the comorbid pathology examined.

KEY WORD: chronic obstructive pulmonary disease, essential hypertension, vasoactive intestinal polypeptide

Wiad Lek 2019, 72, 7, 1265-1268

INTRODUCTION

Chronic obstructive pulmonary disease at the present stage takes the fourth place among the leading causes of morbidity and mortality in the world [1]. According to prognostic data, the prevalence of COPD will increase in the coming decades, which is a consequence of the impact of risk factors and demographic aging of the population. According to the Central Intelligence Agency for 2018, the average age of the total population of Ukraine is 72.4 years. The birth rate of the population is 10.1/1,000 of the population, and the death rate is 14.3/1,000 of the population, ranking 190th place in the world statistics and 6th one, respectively [2]. Considering that the highest prevalence of COPD is observed among adults over 40 years old, it is often in comorbidity with other diseases "acquired" by this age. Most often COPD is associated with diseases of the cardiovascular system, in particular with essential hypertension (EH). In the structure of the incidence, the combination of COPD and hypertension is up to 40% [3].

Currently, COPD is a disease with significant extrapulmonary manifestations. It is assumed that the enhancement of local inflammation in the bronchi, pulmonary parenchyma and vessels has a systemic effect and contributes to the progression of COPD, development of atherosclerosis and cardiac pathology in these patients [4]. At the present stage of work, many of the authors are devoted to the study of such a molecule as a vasoactive intestinal polypeptide (VIP). This neuropeptide is distributed in the central and peripheral nervous systems. It is widely expressed in all structures of the lungs, including the epithelial cells of the respiratory tract, smooth muscle cells of the respiratory tract and lungs, secretory glands and immune and inflammatory cells, mediates relaxation of the smooth muscles of the respiratory tract and blood vessels. Also, the role of VIP in the development of pulmonary hypertension in COPD and its influence on the development of cardiac pathology is actively considered. However, the question of the role of VIP in the course of COPD in combination with EH remains not completely understood.

THE AIM

The aim of our study was to study cardiopulmonary parameters in patients with chronic obstructive pulmonary disease with concomitant hypertension, depending on the level of vasoactive intestinal peptide.

Table I. Mean spirometric and hemodynamic values in patients with COPD, depending on the VIP level

Parameter	VIP 1st tertile (n=33)	VIP 2nd tertile (n=33)	VIP 3rd tertile (n=33)
FEV1,%	57.9 [56;60]* **	59.4[56;63]	60.4 [57;64]
VC%	63.3[62;65]* **	64.3[63;66]	64.7 [62;67]
FEV1,/FVC,%	72.4[69;75]	72.6[70;75]	73.8 [70;77]
Duration of COPD, years	8.0 [6;10]*	8.7 [7;10]	9.6 [8;10]
SBP, mm Hg	140.3 [135;145]* **	131.6 [120; 140]***	125.9 [120;130]
DBP, mm Hg	85.1 [80;90]* **	82.1 [80;80]***	79.5 [80;80]
HR, beats / min	74.1 [70;78]	73.3 [70;78]	73.8 [70;76]
TC, mmol / L	8.7 [7.2;10.3] * **	7.2 [5.8;8.9]***	5.2 [4.3;6.3]
TG, mmol / L	6.6 [5.2;8.0] * **	4.7 [3.1;6.1]***	2.2 [1.4;3.1]

Note: * - the difference between groups of patients of the 1st and 3rd tertile is significant, $p < 0.05$; ** - difference between groups of patients of the 1st and 2nd tertile is significant, $p < 0.05$; *** - difference between groups of patients of the 2nd and 3rd tertile is significant, $p < 0.05$.

MATERIALS AND METHODS

To achieve the objectives we examined 99 patients with COPD GOLD 2; 54 of whom had concomitant EH of II degree. All patients were examined and treated at the Clinics of Scientific-Research Institute of Labour Hygiene and Occupational Diseases of KNMU. The age of patients ranged from 39 to 68 years, the median was 55.0 years. All patients gave written consent to participate in the study. The diagnosis and severity of COPD were established according to the criteria set forth in GOLD working team report (Global Initiative for Chronic Obstructive Lung Disease, update 2015) [5]. At the time of observation, all patients were in the state of remission. On the basis of the order of the Ministry of Health of Ukraine No. 384, dated May 24, 2012, patients were diagnosed with a confirmed diagnosis of EH of II stage. The study did not include patients with concomitant diseases of the respiratory system.

Blood for biochemical and enzyme immunoassays was taken from the cubital vein in the morning on an empty stomach.

Determination of VIP level in the serum of patients was carried out by ELISA using a commercial test system from RayBio (Italy) on the Labline-90 (Austria) immunoassay. The levels of total cholesterol and triglycerides were determined on a LabLine-80 biochemical analyzer from Labline Diagnostics (Austria) using Cone-Lab and Roche reagents (Sweden). The function of external respiration was determined using the SPIROCOM spirographic complex. The generally accepted parameters were determined: VC - vital capacity of the lungs; FEV1 — forced expiratory volume in the first second; FEV1/FVC - Tiffno index.

Statistical analysis of the data was performed using non-parametric statistics. In the samples with non-parametric data distribution, the results are presented as Me (Q25; Q75), where Me is the median (50th percentile), Q25 and Q75 are the 25th and 75th percentile, respectively. To assess the degree of dependence, the Spearman rank correlation coefficient was used. To compare the results, the Mann-Whitney test was used. The null hypothesis was rejected at a confidence level ($p < 0.05$).

RESULTS AND DISCUSSION

All patients with hypertension were divided into tertiary depending on the level of VIP in fasting serum: 1st tertile (n = 33) - the VIP level ranged from 9.5 ng / l to 12.8 ng / l; 2nd tertile (n = 33) - the VIP level ranged from 15.8 ng/l to 18.7 ng/l; 3rd tertile (n = 33) - VIP level ranged from 25.5 ng/l to 30.5 ng/l. Comparative analysis of mean spirometric parameters (VC, FEV1, FEV1/FVC), systolic blood pressure (CBP), diastolic blood pressure (DBP), heart rate (HR), total cholesterol (TC) and triglycerides (TG), The duration of COPD in the examined patients, depending on the VIP level, is presented in Table I.

Comparing the mean values of spirometric parameters (FEV1, FVC) of the first and second and third tertiles, it was found that their values significantly decrease in parallel with the decrease of the VIP level. The FEV1 values are significantly lower in the first tertile than in the second and third ($p < 0.05$). No significant change in the Tiffno index was found. Parameters in all groups were slightly reduced. The duration of the course of COPD was also significantly lower in the first tertile compared to the third ($p < 0.05$).

Analysis of hemodynamic parameters (SBP, DBP) revealed that with a decrease in the level of VIP in the blood serum of the examined, these indicators significantly increase ($p < 0.05$). In patients of the first tertile, SBP incraese was detected in 23 patients (69.6%) and DBP in 13 patients (39.3%). In patients of the second tertile, 23 (36.3%) patients had increased systolic blood pressure and 6 (18.1%) patients had increased DBP. Patients in the third tertile had no increase of SBP and DBP. Significant changes between the tertili in the heart rate were not observed.

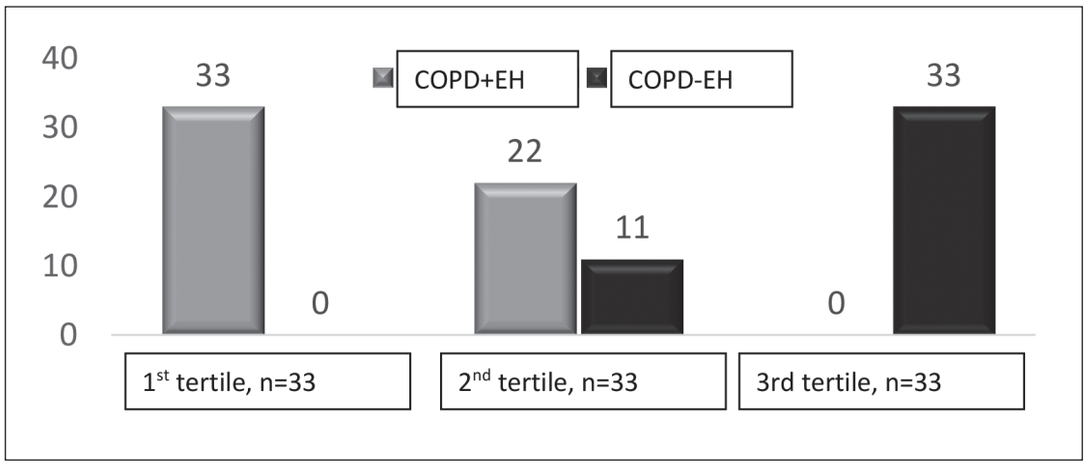


Fig.1. The presence of EH in patients with COPD in the tertiles, depending on the level of VIP.

The number of patients with COPD who had concomitant EH, depending on the level of VIP is presented in the diagram (Fig. 1).

Thus, the diagram shows that with a decrease in the VIP level, the number of patients with essential hypertension increases.

The data obtained in our study may indicate a deterioration of spirographic parameters, respectively, a decrease in the VIP level. In the first tertile, a strong direct correlation between VIP and FEV1 ($r = 0.4$, $p < 0.05$) and FEV1/FVC ($r = 0.39$, $p < 0.05$) was detected, as well as with the duration of COPD ($r = 0.39$, $p < 0.05$). It is known that the functions of VIP, as a neurotransmitter, consist in broncho-and vasodilation. However, with respect to COPD, it does not realize its actions, due to its localization mainly in the major airways [6]. On the other hand, according to the literature data, VIP inhibits apoptosis of alveolar cells, and therefore inhibits the development of the disease [7,8]. In our study, we obtained results showing that a decrease in the level of VIP has a negative effect on spirometric parameters and contributes to an earlier development of COPD.

Also, during the general correlation analysis, the influence of VIP on the formation of atherosclerosis and hypertension in patients with COPD was revealed. A negative strong bond between VIP and TC ($r = -0.54$, $p < 0.05$), TG ($r = -0.72$, $p < 0.05$), SBP ($r = -0.49$, $p < 0$, 05) and DBP ($r = -0.35$, $p < 0.05$) was establishmed. VIP is a neuropeptide that has strong anti-inflammatory effect and performs vascular and cardioprotective functions and regulates the inflammatory response at several levels. Thus, in [9], it was proved that in simulating chronic atherosclerosis in mice, VIP exerted a protective effect reducing the number and size of atherosclerotic plaques and lowering cholesterol levels; thus, reducing the remodeling of blood vessels that is observed with the progression of atherosclerosis. In our work, an association between low VIP level and TC and TG content and with high numbers of SPD and DBP in the first tertile was found, which in our opinion, as perivascular inflammation, can be considered as single pathological link in the development of COPD and EH in the pulmonary and peripheral vascular network.

CONCLUSIONS

Thus, it was revealed that low levels of VIP in the serum of the examined patients had a significant impact on cardiopulmonary parameters. It was proved that if it decreased, the lung ventilation function decreased, systemic inflammation progressed due to the influence of VIP on lipid metabolism; and arterial hypertension is progressed.

Patients of the first tertile with the lowest VIP level showed a significant decrease in FEV1 and VC and the duration of COPD course.

All patients of the first tertile had concomitant hypertension; and blood pressure levels (CBP, DBP) were significantly higher than in patients of the second and third tertiles.

The maximum values of the lipid profile (TC, TG) in patients of the first tertile were identified and they differed significantly from their level in the second and third tertiles.

Considering the revealed interrelationship of VIP with cardiopulmonary parameters, we believe that VIP can also be considered a diagnostic marker as a therapeutic target for COPD with concomitant essential hypertension.

REFERENCES

1. World health organization. The top 10 causes of death. Fact sheet, updated January 2017. Available from: http://apps.who.int/mediacentre/factsheets/fs310/en/index.html
2. Central Intelligence Agency. The world factbook. Available from: https://www.cia.gov/library/publications/resources/the-world-factbook/geos/up.html
3. Frits M.E., Rochester F., Rochester C. Comorbidities in patients with COPD and pulmonary rehabilitation: do they matter? Eur Respir Rev. 2014;131:131-141.
4. Vijayan V.K. Chronic obstructive pulmonary disease. Indian J Med Res. 2013; 137(2):251–269.

5. Mathioudakis AG , Chatzimavridou-Grigoriadou V., Evangelopoulou E et al. Vasoactive Intestinal Peptide Inhaled Agonists: Potential Role in Respiratory Therapeutics. Hippokratia. 2013;17(1):12–16.
6. Onoue S, Ohmori Y, Endo K et al. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide attenuate the cigarette smoke extract-induced apoptotic death of rat alveolar L2 cells. Eur J Biochem. 2004;271(9):1757-67.
7. Misaka S, Sato H, Aoki Y et al. Novel vasoactive intestinal peptide derivatives with improved stability protect rat alveolar L2 cells from cigarette smoke-induced cytotoxicity and apoptosis. Peptides. 2011;32(2):401-7.
8. Benitez R, Delgado-Maroto V., Caro M et al. Vasoactive Intestinal Peptide Ameliorates Acute Myocarditis and Atherosclerosis by Regulating Inflammatory and Autoimmune Responses. The Journal of Immunology. 2018. 200(11):3697-3710.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Olga V. Istomina
9/1 Aptekarskiy lane, app. 46
Kharkiv 61001, Ukraine
tel: +380503011107
e-mail: missistominaolga@gmail.com

Received: 02.02.2019
Accepted: 11.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

FEATURES OF ENDOTHELIUM MORPHOLOGICAL STRUCTURE IN KIDNEY VESSELS, CORONARY ARTERIES AND AORTA DURING CHRONIC KIDNEY DISEASE

Ivan I. Topchii[1], Alexander N. Kirienko[1], Denis A. Kirienko[2], Iryna I. Yakovtsova[4], Alla A. Gavriluk[3], Svitlana V. Danyliuk[4], Igor V. Ivakhno[4], Vira D. Tovazhnianska[4]

[1]GOVERNMENT INSTITUTION "L.T. MALAYA THERAPY NATIONAL INSTITUTE OF THE NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE", KHARKIV, UKRAINE
[2]STATE INSTITUTION "ZAYCEV V.T.INSTITUTE OF GENERAL AND URGENT SURGERY OF NAMS OF UKRAINE", KHARKIV, UKRAINE
[3]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSYA, UKRAINE
[4]KHARKIV MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KHARKIV, UKRAINE

ABSTRACT

Introduction: Vascular endothelium function interruption has the main role among mechanisms of development and progression of chronic kidney disease. In numerous experimental and clinical studies, it was proved that activated vascular endothelium is a structural and functional unit that matches processes of inflammation with intravascular coagulation, fibrinolysis and haemorheological disorders.

The aim: To identify special features of endothelium morphological structure in kidney vessels, coronary arteries and aorta during chronic kidney disease.

Materials and methods: Based on autopsy materials, we conducted a morphological study of patients (n = 20) aged 45 to 55 years who were observed in cardiac and neurological hospitals for 5-7 years. We removed kidney, heart and aorta samples from patients. For the study, a histological and immunohistochemical methods were used.

Results and conclusions: Morphological study of vessels endothelium of kidneys, heart and aorta demonstrated that in the majority of observations intima underwent profound pathological changes, manifested by different degrees of disorganization of endothelial lining and violations of structural and functional organization of the endotheliocytes, subendothelial layer, basal membrane. These pathological processes in all cases had similar features with the development of immune inflammation. Inflammatory infiltration was represented by macrophages, mast cells, plasma cells. Biological mediators of the presented cells can aggravate the damage to endothelial cells. Indirect signs of low ability to restore the structure of the vessel wall and endothelial lining may be a weak expression of the VEGF and bcl-2 vascular endothelial growth factor.

KEY WORDS: Chronic kidney disease, vessels, endothelium disfunction, immune inflammation

Wiad Lek 2019, 72, 7, 1269-1273

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem. The number of people with CKD who receive dialysis therapy and patients after kidney transplantation has increased from 340,000 in 1999 to 651,000 in 2010, and this amount is increasing each year [1, 2].

Despite success in researches for effective ways of treatment in recent years, CKD remains one of the most severe and prognostically unfavorable diseases [3, 4].

Vascular endothelium function interruption has the main role among mechanisms of development and progression of CKD, as in kidney, so in all vessels. In numerous experimental and clinical studies, it was proved that activated vascular endothelium is a structural and functional unit that matches processes of inflammation with intravascular coagulation, fibrinolysis and haemorheological disorders [5, 6].

In modern literature, endothelium is considered not only as a barrier between blood and tissues, but also as a neuroendocrine organ that performs many functions, by developing pro- and anti-inflammatory factors, vasodilating and vasoconstrictor substances, pro- and antiaggregants, pro- and anticoagulants, - and antifibrinolytic agents, proliferation factors and growth inhibitors. In addition, endothelium has its own renin-angiotensin system [7, 8, 9].

Thus, endothelium can affect systemic arterial pressure (SAP). Under physiological conditions, vasodilation the synthesis of aggregation inhibitors, coagulation and activators of fibrinolysis, antiadhesive substances predominate. Vascular cell dysfunction disrupts this balance and predisposes vessels to vasoconstriction, leukocyte adhesion, platelet activation, mitogenesis, inflammation [10, 11, 12].

Endothelial dysfunction was originally defined as a violation of vasodilation in response to specific stimuli, such as acetylcholine and bradykinin. In a broader sense, this term may include not only violation of va-

sodilation, but also pro-inflammatory and pro-thrombogenic states associated with endothelial dysfunction [13, 14, 15].

The study of morphological features of CKD has great medical and social importance and requires further scientific research.

THE AIM

To identify special features of endothelium morphological structure in kidney vessels, coronary arteries and aorta during chronic kidney disease.

MATERIALS AND METHODS

Based on autopsy materials, we conducted a morphological study of patients (n = 20) aged 45 to 55 years who were observed in cardiac and neurological hospitals for 5-7 years. The main diagnosis was ischemic heart disease on the background of signs of chronic glomerulonephritis and pyelonephritis. The main cause of death was acute heart failure (n = 15), acute impairment of cerebral circulation in form of ischemic infarcts (n = 2), acute myocardial infarction (n = 3).

We removed kidney, heart and aorta samples from patients, then samples were fixed in 10% formalin, and then poured into paraffin. For the study, a histological method was used: staining with hematoxylin and eosin for observational microscopy.

To identify characteristics of immune cell reactions in inflammatory process zones we used primary monoclonal antibodies (MCAB) from DAKO (Denmark), Ready-to-Use. We revealed expression of T- and B-cell differentiation clusters (CD3, CD20), marker of plasma cells (CD38), macrophage marker (CD68) using immunohistochemical method. Features of endothelialization of intimal vessels were studied by expression of endothelial cells marker (CD31 JC 70A), tendency to vascularization was assessed using vascular endothelial growth factor (VEGF (VG1)). As marker of apoptosis, bcl-2 (124) was used.

Material for immunohistochemistry study was fixed with 10% neutral formalin for 24 hours, poured into paraffin, 4 microns thick sections were prepared which were applied to Super Frost high-adhesive slides and dried at 37 ° C for 18 hours. Demasking heat treatment was performed by method of boiling sections in citrate buffer (pH 6.0). To visualize the primary antibodies, the UltraVision Quanto Detection Systems HRP Polymer (Thermo scientific) was used. We also used DAB (diaminobenzidine) as chromogen.

To mark severity of the immunohistochemical label, a semiquantitative scale was used: + - weak, ++ - moderate, +++ - severe reaction. The complex of morphological studies was carried out using the Primo Star microscope (Carl Zeiss) using the AxioCam (ERc 5s). Our study was conducted according to conditions specified in the methodical recommendations of Ministry of Health of Ukraine, and the ethical principles of WMA Declaration of Helsinki ethical principles for medical research involving human subjects. (Conclusion of ethical commission of KhMAPO №1 from 9.01.2014).

RESULTS

In each observation, histological structure of kidneys had its own features. In most cases, on the background of diffuse congestion of cortical and cerebral layers we found erythrostasis, diapedemic hemorrhages and moderate edema. There was also congestion of glomeruli and areas of shrinkage in kidneys' parenchyma in form of atrophy and sclerosis. In tubules epithelium protein dystrophy, zones of necrobiosis of individual epithelial cells and small groups of cells were observed. We also observed focal and, in places, diffuse lymphohistiocytic infiltration of stroma. We also found groups of tubules in state of thyroidization.

The walls of most vessels were defibrated and unevenly thickened due to foci of moderate and severe sclerosis. The intimas' endotheliocytes of vessels and capillaries were flattened. In some of the vessels we revealed detachment of endotheliocytes and destruction of vessels' wall. In some cases, desquamation and focal necrosis of the endothelium with poorly expressed polynucleic infiltration were revealed. There was also an increase in heterogeneity and a decrease in ordering of cells location, which, in our opinion, caused a low degree of endotheliocyte binding among themselves and, in turn, leads to an increase in permeability of the vascular wall.

We obsereved presence of pycnotic nuclei, nuclei with karyorexis and karyolysis, a microplasmatosis in many cells. Besides, the expression of bsl-2 could be assessed as moderate and even severe (+++), though in tubule epithelial cells cytoplasm, in the kidney vessels intima, endotheliocytes of the glomerular capillaries, it was negative (-). We regarded this data as a manifestation of oxidative stress and inability to restore the endothelial layer integrity (Figure 1).

The level of VEGF expression in vessels walls structures of the kidneys showed a similar pattern: the endothelial growth factor either did not appear at all, or showed as weak (+), and in isolated cases, moderate (++) immune response.

In our study, the inflammatory infiltrate was defined as moderate and, in some places, severe - from 4-8 to 10-12 mononuclears in the x400 field of view. In some observations, lymphoid cells predominated, with CD3 + status. In some cases, a large number of plasma CD38 + cells were observed in the interstitium. Many of them demonstrated holocrine type secretion and we observed clasmatosis, which is a morphological reflection of humoral immunity activity. CD20 + lymphocytes, CD68 + macrophages and mast cells, as well as plasmocytes in the kidney stroma were detected.

In myocardium samples, we observed signs of acute cardiac death. In all cases, uneven coloration of cardiomyocytes was detected, some muscle fibers lost transverse

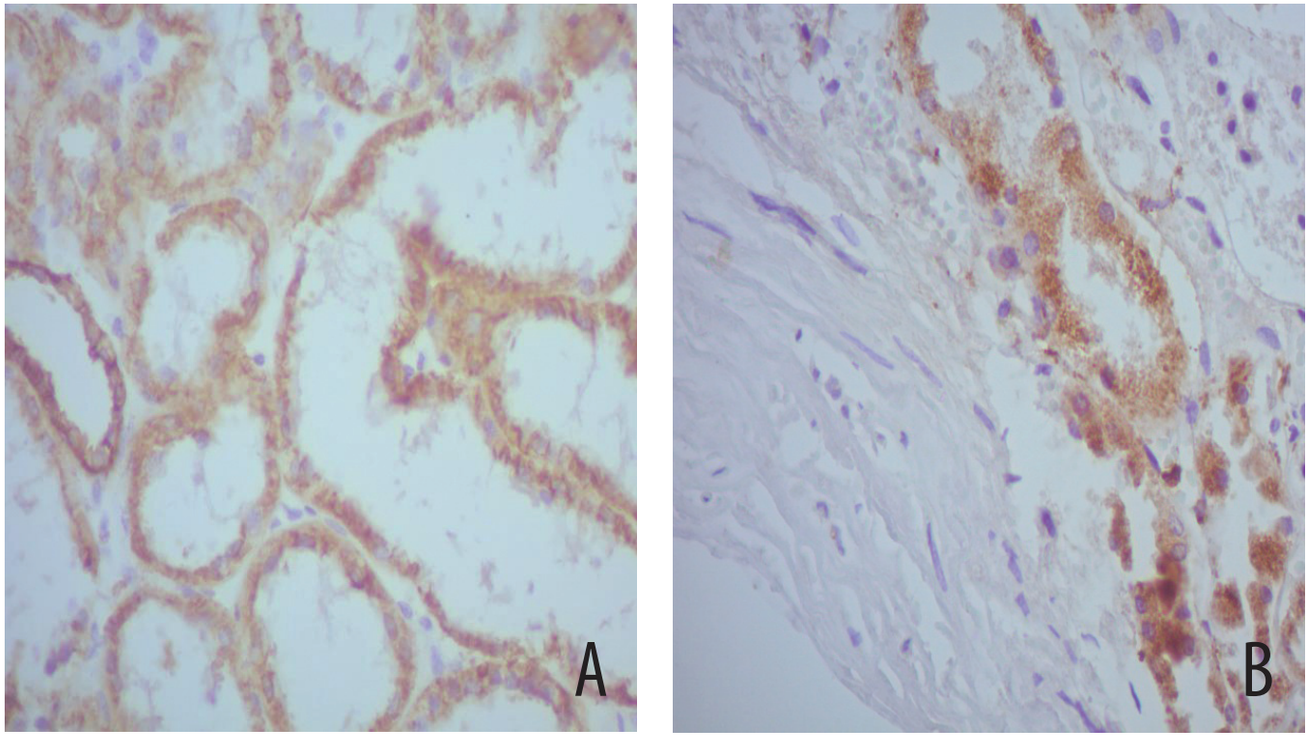


Fig. 1. Severe cytoplasmic expression of bcl-2 in the renal tubular epithelial cell group (A), absence of bcl-2 expression in vessel wall structures (B). Reaction with bcl-2 (124), x400

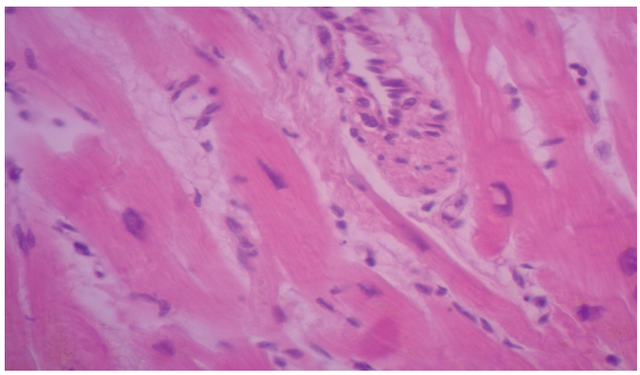


Fig. 2. Lipoidosis in small branch of coronary artery with disseminated inflammatory infiltration, frequent conduction of endothelium. Stained with hematoxylin and eosin, x400.

striation and expressed eosinophilia. Multiple contractures and sections of decomposition of myofibrils, small foci of fragmentation, areas of undulating deformation of myocardial muscle fibers were observed. Interstitium showed edema, with development of its basophilia. There was observed protein dystrophy of cardiomyocytes, subtotal moderate-expressed hypertrophy, mild lipofuscinosis of cardiomyocytes' cytoplasm.

Signs of spasm and endothelial dysfunction were observed in main trunks of coronary arteries and in their large branches showed. They manifested themselves in the "chalky" location of the endothelium, contours falsity of arteries, infringement of smooth muscle fibers drawn

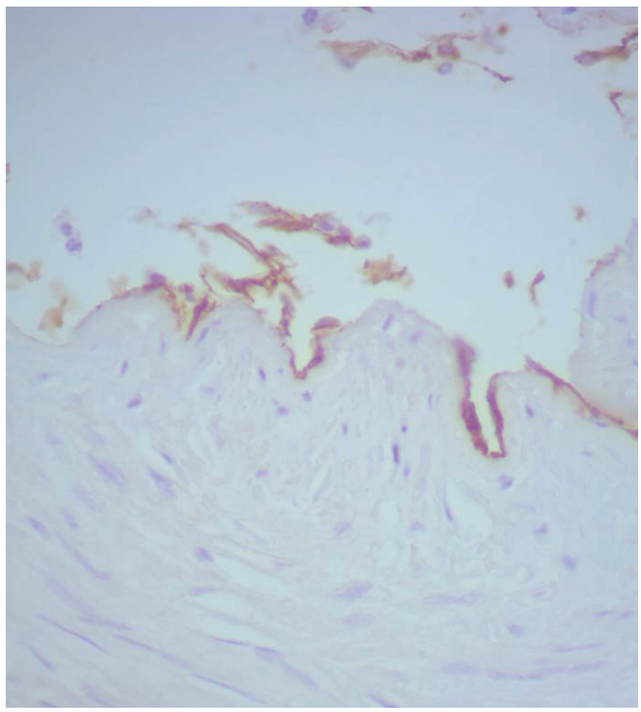


Fig. 3. Weak, uneven expression of CD31 in coronary arteries endothelium. Reaction with MKAT CD31 JC 70A, x400.

in them, plasma penetration, and thrombus formation zones. We could see narrowing of arteries, exfoliation of the endothelium in small branches; sometimes under it were

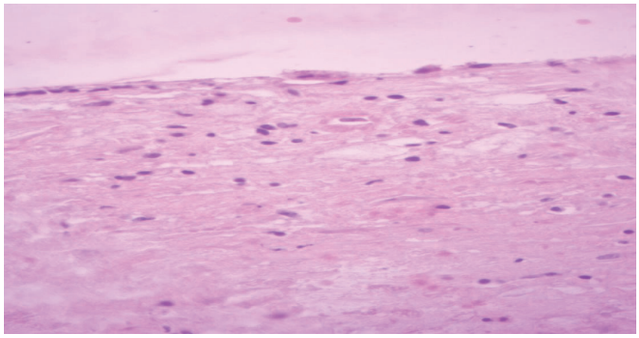


Fig. 4. Aorta intima: enlargement and desquamation of endotheliocytes, swelling of the subendothelial layer. Stained with hematoxylin and eosin, x400.

found erythrocytes or clusters of plasma. In a number of myocardium areas, vessels, especially capillaries and small veins, had different degrees of blood filling: some - sharply expanded, full of blood, others - not. In dilated capillaries, stasis, erythrocyte sludge was found, and many diapedemic hemorrhages were identified perivascularly.

In some observations, small and single-sized coronary arteries with uneven wall thickening were presented due to initial (at the stage of lipoidosis) coronarosclerosis. It is narrowed, in the wall - with moderate perivascular productive inflammation (Figure 2).

Reaction with endothelial cells marker showed disturbances in endothelialization of coronary arteries intima. It was weak, uneven, with the exposure of wide intercellular contacts (Figure 3), while the myocardial vascularization was sufficient - 3-5 capillaries per cardiomyocyte (Figure 3).

Cellular infiltration both in arteries walls and in myocardium stroma was extremely meager. In myocardium, positively stained cells were located singly in the interstitium, sometimes perivascularly and showed plasma cell differentiation (CD38 +). In the coronary arteries intima and their branches, the inflammatory infiltrate was detected in the zones of edema, destruction of the vessel wall, and in it CD68 + granulocytes-macrophages and mast cells predominated.

Endothelium, subendothelial layer, plexus of elastic fibers were clearly visualized in aorta inner wall. The endothelium consisted large (up to 500 μm in length and 150 μm in width) flat single-nucleated, often multi-nucleated, polygonal cells located on the basal membrane. The areas of vascular cells enlargement, pockets of desquamation were found. The subendothelial layer was well developed, formed by a loose fibrous connective tissue, which contained thin collagen and elastic fibers, many amorphous substances and non-differentiated cells such as smooth muscle fibroblasts, macrophages. Almost all observations revealed areas of edema, deformation, deposition of cholesterol and fatty acids. Vasa vasorum in this layer were absent (Figure 4).

The reaction of endothelial cells with CD31 was quite severe, was detected in almost every cell, which differed in different sizes and shapes, formed protrusions and indentations and showed extended intercellular contacts.

The number of inflammatory cell elements in aortic wall was small, the qualitative composition of infiltrate, its location was similar to the coronary arteries intima.

It was difficult to judge the nature of apoptosis only indirectly by reaction with the vascular endothelial growth factor and bcl-2, since apoptotic bodies in coronary arteries and aorta cells intima were not detected. Features of the reaction with the growth factor of the endothelium resembled those in the arterioles and large vessels of kidneys - expression was moderate, in some vessels it was weak, it was detected as tender granules, clumps in endothelial cells, fibroblasts, macrophages. The anti-apoptosis protein bcl-2 in these structures was not detected.

DISCUSSION

Immunocompetent cells, which are main components of immune system, are involved in implementation of inflammation and formation of immune response in CKD patients [16]. In our material, single CD20 + lymphocytes, CD68 + macrophages and mast cells and more numerous plasma cells were found mainly in perivascular space. The very similar data were observed in Spatola L. et al. study in 2019 [17].

In myocardium samples with hematoxylin and eosin staining, we observed signs of acute cardiac death, with presence of focal damage of cardiomyocytes. Signs of spasm and endothelial dysfunction were found in main trunks of coronary arteries and in their large branches. The reaction with the CD31 endothelial cell marker more clearly demonstrated uneven intimal endothelialization in coronary arteries. Morgado-Pascual J.L. et all (2018) observed, that common mechanisms involved in CKD, including oxidative stress, inflammation, and uremic toxins, can contribute to renal damage progression by inducing epigenetic modifications [18].

Vascular endothelial growth factor (VEGF) is a biologically active substance, which binds and activates membrane receptors; triggers a signaling cascade that stimulates growth and proliferation of endothelial cells [19]. After new vessels formation, VEGF acts as a survival factor through suppression of endotheliocytes apoptosis. Level of VEGF expression in vascular walls showed a similar picture: either it was not detected at all, or showed a weak, and in isolated cases, a moderate response [20].

Apoptosis plays a decisive role in pathogenic factors that affect cell viability under traumatic effects [21]. One of main participants in cell death program implementation is bcl-2 protein, which blocks mitochondrial pathway for start of apoptosis. The cell is retained at certain points of cell cycle for possible repair of damage or undergoes apoptosis due to a violation of mitochondrial and nuclear membranes permeability. Agents such as calcium ions, inflammation factors, free radicals, and nitrous oxide can also "turn on" genes that initiate apoptosis [22]. In our study bcl-2 expression in vascular intima was weak or negative, which we regarded as a manifestation of oxidative stress and inability to restore the integrity of endothelial layer.

CONCLUSIONS

Morphological study of vessels endothelium of kidneys, heart and aorta demonstrated that in the majority of observations intima underwent profound pathological changes, manifested by different degrees of disorganization of endothelial lining and violations of structural and functional organization of the endotheliocytes, subendothelial layer, basal membrane.

These pathological processes in all cases had similar features with the development of immune inflammation. Inflammatory infiltration was represented by macrophages, mast cells, plasma cells. Biological mediators of the presented cells can aggravate the damage to endothelial cells. Indirect signs of low ability to restore the structure of the vessel wall and endothelial lining may be a weak expression of the VEGF and bcl-2 vascular endothelial growth factor. In conditions of their lack, prerequisites for the activation of apoptosis are created.

REFERENCES

1. Levey AS, Coresh J, Balk E, Kausz AT et al. National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Clinical guidelines. 2003:137-147.
2. Kopyt NR. Chronic kidney disease: the new silent killer. JAOA. 2006;106(3):133-136.
3. Heijnen T, Wilmer A, Blockmans D et al. Outcome of patients with systemic diseases admitted to the medical intensive care unit of a tertiary referral hospital: a single center retrospective study. Scandinavian Journal of Rheumatology. 2016;45(2):146-150.
4. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature. 1980;288:373–376.
5. Kvietys PR, Granger DN. Endothelial cell monolayers as a tool for studying microvascular pathophysiology. American Journal of Physiology. Gastrointestinal Liver Physiology. 1997;273:1189–1199.
6. Verma S, Anderson TJ. Fundamentals of endothelial function for the clinical cardiologist.Circulation. 2002;105:546–549.
7. Schiffrin EL. A critical review of the role of endothelial factors in the pathogenesis of hypertension. Journal of Cardiovascular Pharmacology. 2001;38:3–6.
8. Cines DB, Pollak ES. Endothelial Cells in Physiology and in the Pathophysiology of Vascular Disorders. Blood. 1998;91(10):3527–3561.
9. Wilhelmus S., Alpers CE, Cook HT. et al. The Revisited classification of GN in SLE at 10 years: Time to reEvaluate histopathologic lesions. Journal American Society of Nephrology. 2015;26;№ 12:29382946.
10. Shlipak MG, Fried LF, Crump C, et al. Cardiovascular disease risk status in elderly persons with renal insufficiency. Kidney International. 2002;62:997-1004.
11. Van N, Amerongen GP, Vermeer MA, et al. Simvastatin improves disturbed endothelial barrier function. Circulation 2000;102:2803-09.
12. Sorokin A, Kohan D. Physiology and Pathology of endothelin-1 in renal mesangium. AJP Renal Physiology.2003;285:579-589.
13. Shao-Bin Duan, Liu FY, Luo JA. et al. Assessment of urinary endothelin-1 and nitric oxide levels and their relationship with clinical and pathologic types in primary glomerulonephritis. Yonsei Medical Journal. 1999;40:425-429.
14. Kang D.H., Kaneiiis J., Hugo C. Et al. Role of microvascular en-dotelium in progressive renal disease.// J. Am. Soc. Nephrol. 2002; 13: 806-816.
15. Ferrante A, Guggino G, Di Liberto D et al. Endothelial progenitor cells: Are they displaying a function in autoimmune disorders? Mechanisms of Ageing and Development. 2016;3;№ 5:122-128.
16. Toprover M, Crittenden DB, Modjinou DV, et al. Low-Dose Allopurinol Promotes Greater Serum Urate Lowering in Gout Patients with Chronic Kidney Disease Compared with Normal Kidney Function. Bulletin of the Hospital for Joint Disease. 2019;77(2):87-91.
17. Spatola L, Dozio E. Obesity-associated mortality risk: Chronic kidney disease in focus. Nutrition, Metabolism and Cardiovascular Diseases. 2019;29(2):212-213. doi:10.1016/j.numecd.2018.12.002.
18. Morgado-Pascual JL, Marchant V, Rodrigues-Diez R et al. Epigenetic Modification Mechanisms Involved in Inflammation and Fibrosis in Renal Pathology. Mediators of Inflammation. 2018:2931049. doi: 10.1155/2018/2931049. eCollection 2018.
19. Ghaemian A, Yazdani J, Azizi S et al. Remote ischemic preconditioning to reduce contrast-induced acute kidney injury in chronic kidney disease: a randomized controlled trial. BMC Nephrology. 2018;19(1):373. doi: 10.1186/s12882-018-1169-x.
20. Ríos-Silva M, Santos-Álvarez R, Trujillo X et al. Effects of Chronic Administration of Capsaicin on Biomarkers of Kidney Injury in Male Wistar Rats with Experimental Diabetes. Molecules. 2018;24(1). pii: E36. doi: 10.3390/molecules24010036.
21. Burlaka I, Nilsson LM, Scott L et al. Prevention of apoptosis averts glomerular tubular disconnection and podocyte loss in proteinuric kidney disease. Kidney International. 2016;90(1):135-48. doi: 10.1016/j.kint.2016.03.026.
22. Huang YS, Lai JB, Li SF et al. Relationship between Renalase Expression and Kidney Disease: an Observational Study in 72 Patients Undergoing Renal Biopsy. Current Medical Science. 2018;38(2):268-276. doi: 10.1007/s11596-018-1875-4.

The theme of research: «Improve of diagnostic methods and effectiveness of treatment of chronic glomerulonephritis (CGN) and chronic pyelonephritis (CPN) on basis of studying markers of functional state disturbances and damage of vascular endothelium of kidneys». Code 02/12, State registration number 0112U001097. 01.12-12.14. Head of Research Laboratory: professor Topchiy I.I., PhD, MD.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Vira D. Tovazhniaska
Department of Pathological Anatomy
Kharkiv Medical Academy of Postgraduate Education
195 Moskovsky ave., 61000 Kharkiv, Ukraine
tel: +380957593208
e-mail: viratov@yahoo.com

Received: 09.02.2019
Accepted: 03.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

PHARMACOECONOMIC AND EPIDEMIOLOGICAL BASES OF OPTIMAL ROTAVIRUS VACCINE SUPPLY FOR UKRAINIAN POPULATION

Serhii O. Soloviov [1,2], Hennadiy A. Mokhort [3], Olena P. Trokhimenko [1], Hleb V. Zahoriy [1], Viktor V. Trokhymchuk [1], Iryna P. Kolesnikova [3], Iryna V. Dziublyk [1]

[1]SHUPYK NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KYIV, UKRAINE
[2]THE NATIONAL TECHNICAL UNIVERSITY OF UKRAINE "IGOR SIKORSKY KYIV POLYTECHNIC INSTITUTE", KYIV, UKRAINE
[3]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Introduction: Several studies has shown that rotaviruses play a leading role in the structure of acute intestinal infections (AII) of viral etiology in children. In the National vaccination calendar of Ukraine, vaccination against rotavirus infection (RVI) is classified as recommended, with the expected goal of reducing the number of severe RVI cases among under five-year-old children. Nevertheless, despite the positive epidemiological and clinical effects of vaccination against RVI, it remains unclear how appropriate the introduction of rotavirus vaccines is in terms of potential costs and benefits, as well as determining the optimal level of subsidy required to cover part of the costs of voluntary vaccination of the population.

The aim: Study of optimal subsidy level of rotavirus vaccine in Ukraine using epidemiological and pharmacoeconomic modeling.

Materials and methods: The retrospective epidemiological data of the monthly RVI incidence in Ukraine as well as the population number from 2010 to 2016 formed the information basis for determining the transmission parameter of the viral agent. The scenario of RVI epidemic process as an acute intestinal infection from the point of view of mathematical epidemiology is best described by developed mathematical model. Cost-benefit of rotavirus vaccination was studied with the use of developed pharmacoeconomic criteria.

Results and conclusions: Prediction of possible implications of RVI vaccination and finding optimal level of vaccine supply involves a comprehensive study of the epidemic process peculiarities of this infection with development of an adequate epidemiological model. We have proposed a model of RVI epidemiological process in Ukraine, determining its main parameters with the use of available retrospective data of anual number of RVI cases for the period from 2010 to 2016. The developed model was used as an analytical tool for analyzing influence of different levels of vaccine supply on vaccination cost-benefit. The results of research showed that the use of epidemiological modeling in pharmacoeconomic analysis of rotavirus vaccination made it possible to determine analytically optimal level of vaccination subsidy level.

KEY WORDS: rotavirus infection, epidemiological model, vaccination, pharmacoeconomic modeling, subsidy

Wiad Lek 2019, 72, 7, 1274-1280

INTRODUCTION

The problem of acute intestinal infections (AII) global spread is currently relevant [1-3], since they play one of the leading role among infectious diseases after the influenza and acute respiratory diseases [4, 5]. The spectrum of agents causing AII is diverse and includes pathogenic and potentially pathogenic bacteria, protozoa, and viruses [6-8]. Several studies have shown that viruses cause from 25 to 60% of AII cases, among which rotaviruses play a leading role in the structure of children's AII of viral etiology [4, 9, 10]. According to the Global Disease Burden in 2015, rotavirus infection (RVI) remains the leading cause of morbidity and mortality in children aged under five years of age, despite a decrease in the number of admission cases associated with diarrhea and death [11, 12]. Despite the fact that the number of deaths caused by rotavirus gastroenteritis declined from 528,000 in 2000 to 215,000 in 2013, of which over 80% were recorded in Asian and African countries, RVI continues to cause significant damage of public health across the world regardless of the economic development level, causing direct and indirect economic loses, estimated at hundreds of billions of dollars per year [13, 14].

Since 1973 and to date, most authors associate RVI with children, attributing it to the section of pediatric problems. As a result, often adults in the world are not examined for the rotavirus in case of AII. This fact is of fundamental importance, as it leads to a large number of non-detected RVI cases among different age groups [15]. However, despite the active role of adults in rotavirus spread, children aged under 5 years play a dominant role in its clinical structure.

WHO recommends rotavirus vaccination into the national immunization programs in countries with infant deaths of diarrhea > 10%, such vaccination introduced since 2006 in 20 countries in Latin America, the United States, Australia, South Africa, Belgium, Luxembourg,

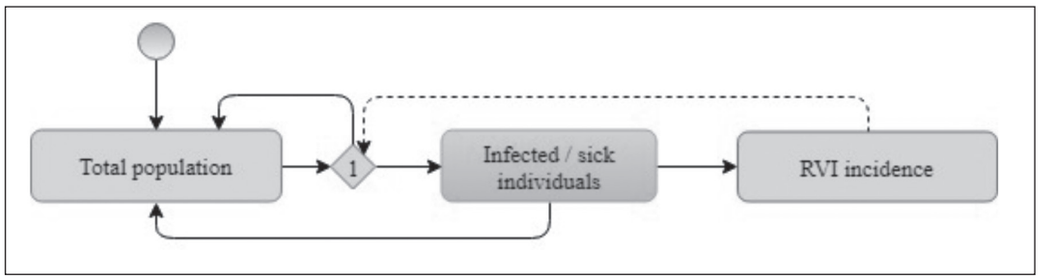


Fig. 1. RVI epidemiological model considering recurrent infection cases.

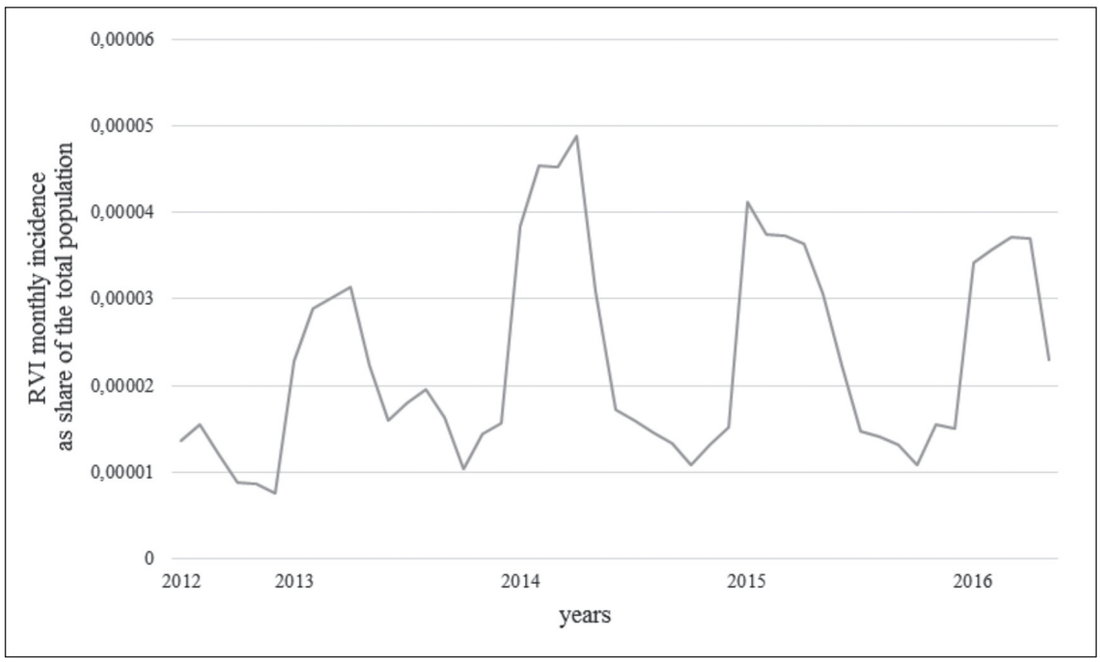


Fig. 2. Monthly RVI incidence during the observational time period.

Austria and Finland, has significantly reduced RVI incidence in these countries [16, 17]. In 2009, WHO recommended to include rotavirus into the list of vaccines for the Expanded Program on Immunization [18]. As of today, two live attenuated peroral rotavirus vaccines are available [19-23]. In the preventive vaccination calendar (MOH Ukraine Order No. 947 dated May 18, 2018), rotavirus vaccination is attributed to recommended vaccinations, wich expected goal of to reduce the number of severe RVI cases among five-year-old children.

Nevertheless, despite the positive epidemiological and clinical effects of vaccination against RVI, it remains unclear how appropriate the introduction of rotavirus vaccines is in terms of potential costs and benefits, as well as determining the optimal level of subsidy required to cover part of the costs of voluntary vaccination of the population.

THE AIM

The aim of research was the study of optimal subsidy level of rotavirus vaccine in Ukraine using epidemiological and pharmacoeconomic modeling.

MATERIALS AND METHODS

The scenario of RVI epidemic process as an acute intestinal infection from the point of view of mathematical epidemiology is best described by the model proposed by W. Kermak and A. Mackendrick in 1927 [24, 25]. According to this model, individuals in the population can be divided into *susceptible* (S) that were not previously exposed to the agent, *infected* (I), that are carriers of infectious agents with manifestation of clinical symptoms or without them, and those *recovered* (R), with acquired specific immunity and subject to the elimination of the pathogen. Since a individual can have RVI several times, especially during the first five years of the child's life, due to the variety of genotypes of circulating rotaviruses and the lack of stable cross-immunity [26], proposed in the literature epidemiological model can be simplified without loss of quality (Fig. 1), given that recovery after infection and elimination of the viral agent is accompanied by an "immediate" return to a group of susceptible individuals and the possibility of a disease re-occurrence caused by rotavirus of another genotype [27]. In this model node (1) denoted probability of RVI, depending on RVI incidence.

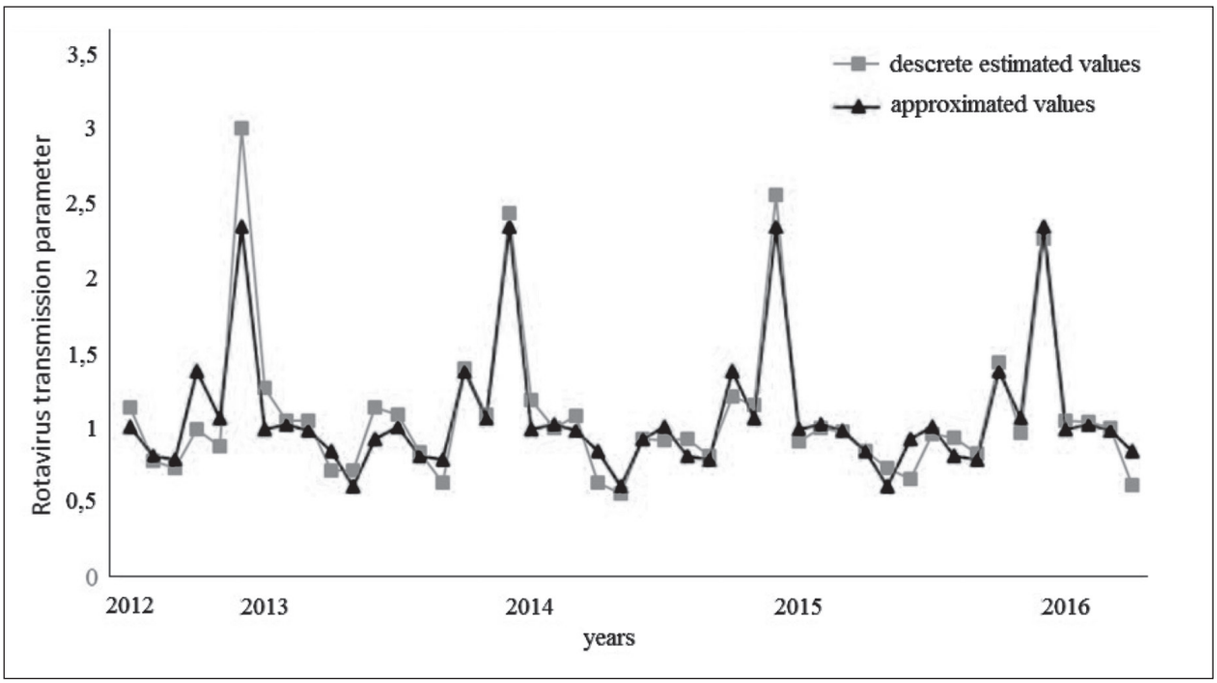


Fig. 3. Rotavirus transmission parameter.

Described epidemiological model can be formalized using next difference equation system:

$$\begin{cases} s_{t+1} = s_t - \beta_t \cdot i_t \cdot s_t + \gamma_t \cdot i_t \\ i_{t+1} = i_t + \beta_t \cdot i_t \cdot s_t - \gamma_t \cdot i_t \end{cases} \quad (1)$$

where s_t – number of susceptible individuals; i_t – number of infected / ill individuals; β_t – rotavirus transmission parameter; γ_t – recovery (infectivity loss) rate.

It was also important to determine the appropriateness of rotavirus vaccination for a certain population group, considering its place in the structure of both susceptible and vaccinated individuals. So, if the proportion of such individuals among the susceptible ones is , and among the infected ones is , then the dynamics of the epidemic process of RVI for such a group will be formally defined making the substitution in eq. 3 for inectious individuals:

$$\frac{i'_{t+1}}{n} = \frac{i'_t}{n} + b_t \cdot i_t \cdot \frac{s'_t}{m} - \gamma_t \cdot \frac{i'_t}{n} \quad (2)$$

$$i'_{t+1} = i'_t + \frac{n}{m}\beta_t \cdot i_t \cdot s'_t - \gamma_t \cdot i'_t \quad (3)$$

where it becomes clear that:

$$\beta' = \frac{n}{m} \cdot \beta \quad (4)$$

In the considered model recovery (infectivity loss) rate is assumed to be equal to one ($\gamma_t = 1$) if the epidemiological observation interval is greater or equal to the average infectious period. The key model parameter is vital agent transmission parameter, which is defined at each time interval as:

$$\beta_t = \frac{I_{t+1} \cdot N_t}{I_t \cdot S_t} \quad (5)$$

Rotavirus transmission parameter was determined using retrospective monthly RVI incidence epidemiological data in Ukraine (Form 3 of Statistical Report) from 2010 to 2016, provided by the Center for Public Health of the Ministry of Health of Ukraine as share of total population (Fig. 2).

Information on asymptomatic RVI cases was unknown, so it was assumed that it has been already included into parameters of the epidemiological model. According to the WHO recommendations, RVI is considered to be severe if patients have symptoms according to the Vesikari grading scale > = 11 [28].

RESULTS AND DISCUSSION

So, using formula (2) it was found descrete and then approximated (smoothed) rotavirus transmission parameter as key factor in RVI incidence prediction (Fig. 3). It is a characteristic of the infectious agent and is supposed to have a seasonal pattern with peak in winter-spring period, which was confirmed by epidemiological observations.

Optimal level of voluntary vaccination coverage could be found by modification of above mentioned epidemiological model, adding class of vaccinated individuals (Fig. 4) into above-described epidemiological model (Fig. 1). Here nodes (1-2) denoted share of Vaccination

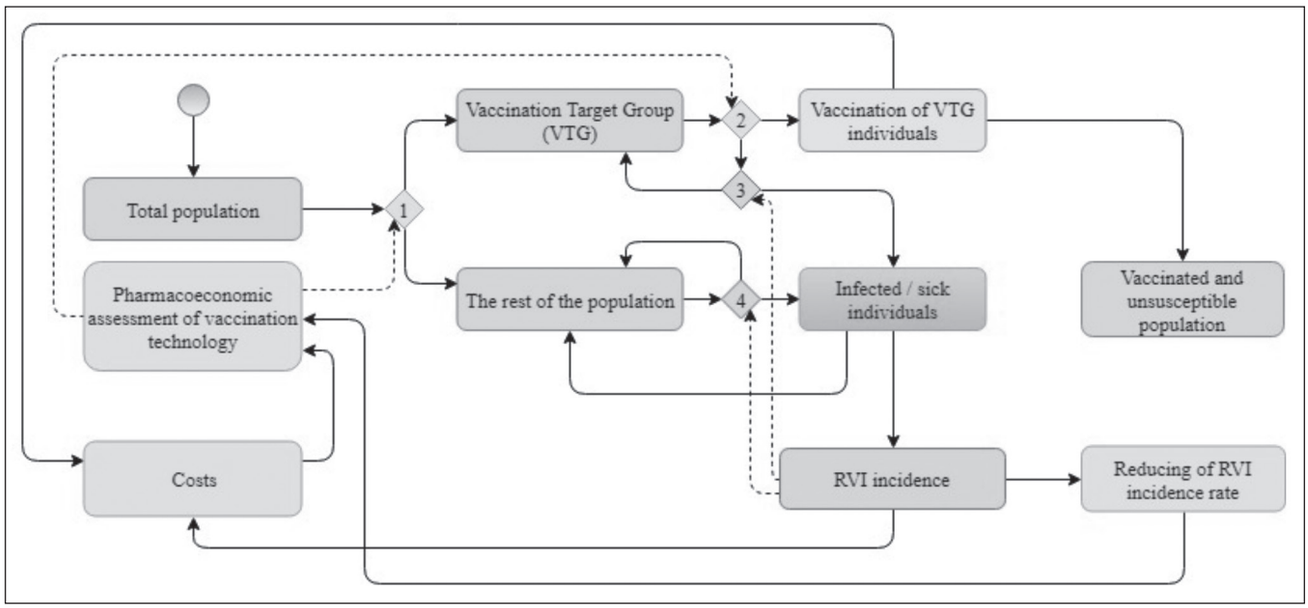


Fig. 4. RVI epidemiological model with vaccination considering recurrent infection cases.

Target Group (VTG) and probability of vaccination in this group respectively. Nodes (3-4) denoted RVI probabilities for VTG and the rest of population, depending on RVI incidence.

Such model was described mathematically using the following system of difference equations:

$$\begin{cases} s_{t+1} = s_t - \beta_t \cdot i_t \cdot s_t + \gamma_t \cdot i_t - \nu_t \cdot s_t \\ i_{t+1} = i_t + \beta_t \cdot i_t \cdot s_t - \gamma_t \cdot i_t \\ v_{t+1} = v_t + \nu_t \cdot s_t \end{cases} \quad (6)$$

where s_t – proportion of susceptible individuals; i_t – proportion of infected / ill individuals; v_t – proportion of vaccinated individuals; β_t – rotavirus transmission parameter; γ_t – recovery (infectivity loss) rate; ν_t – level of vaccination coverage.

From epidemiological point of view marginal vaccine benefit population vaccine benefit (PVB) is determined as a ratio of the total number of prevented RVI cases to the total number of vaccinated individuals was taken as epidemiological effectiveness criteria of vaccine supply:

$$PVB = \frac{\sum_t i_t - \sum_t i_t^v}{\sum_t v_t} \quad (7)$$

where i_t – number of infected / ill individuals *without introduction of* vaccination *at time t*; i^v_t – number of infected

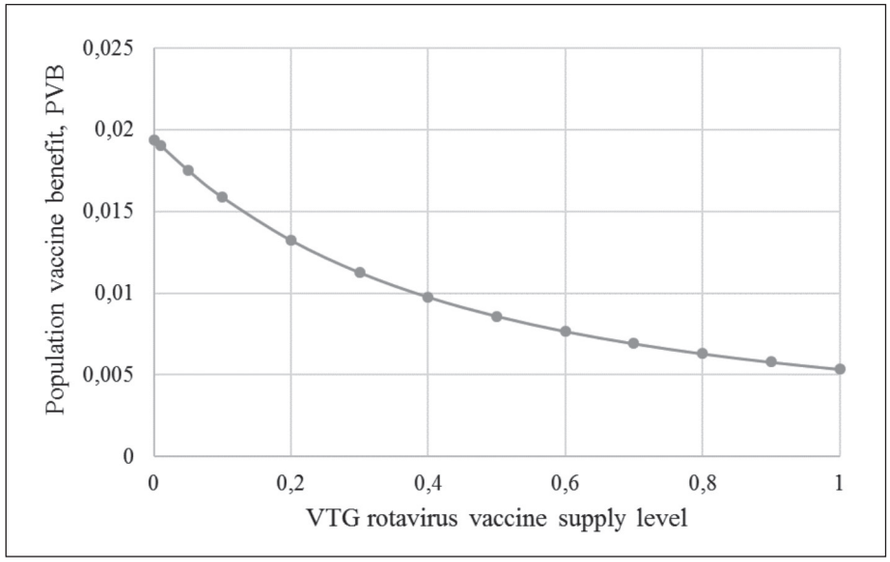


Fig. 5. PVB level

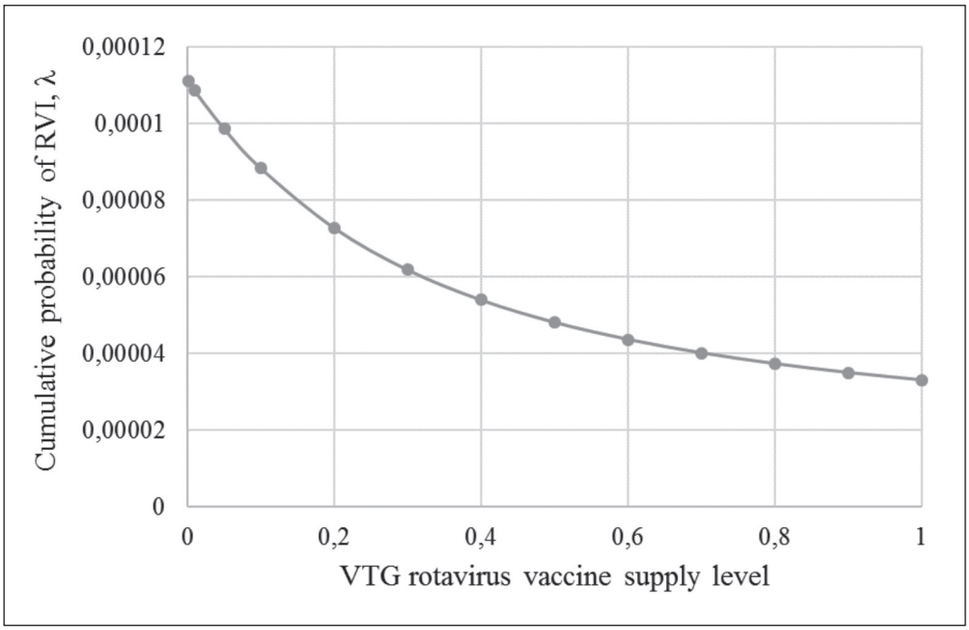


Fig. 6. Cumulative RVI probability

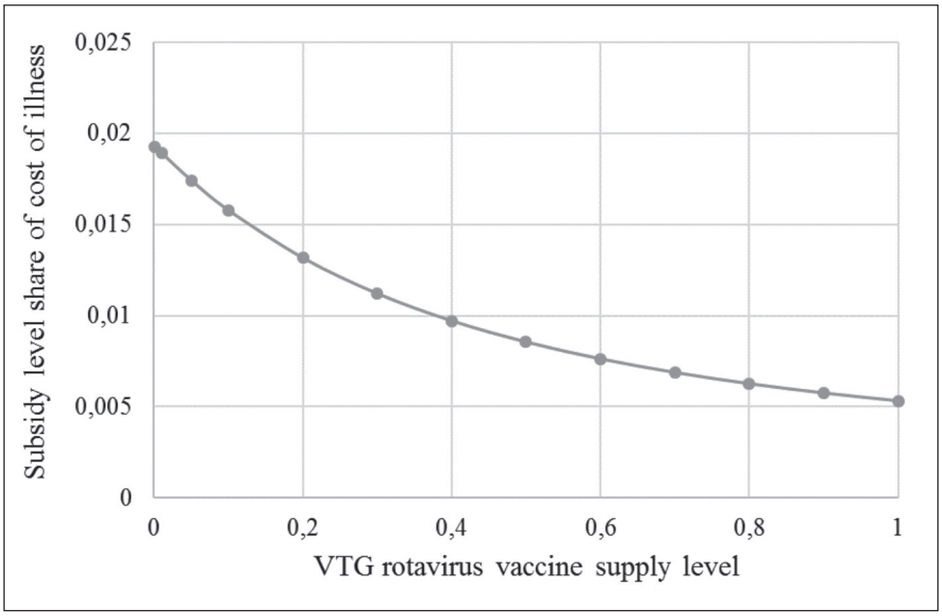


Fig. 7. Potential subsidy level share

/ ill individuals *with introduction of* vaccination *with certain level of vaccine supply at time t*; v_t – number of vaccinated individuals *at time t*.

With introduction of cost of ilness, C_i, and vaccination cost, C_v from pharmacoeconomic perspective total vaccination costs during sertain period of time, $C_v \sum v_t$ must be less than total monetary benefit of prevented RVI cases:

$$C_v \sum v_t < (\sum_t i_t - \sum_t i_t^v) \cdot C_i \quad (8)$$

So, pharmaeconomic rule from social perspective allows estimation of ratio threshold for cost-effective vaccination agains RVI:

$$\frac{C_i}{C_v} > \frac{1}{\text{PVB}} \quad (9)$$

As rotavirus vaccination is voluntary, it is reasonable to analyse it from individual perspective. Rotavirus vaccination would be cost-effective for individual in case of less vaccination costs C_v comparing to expected cost of illness , where is cumulative probability of RVI for one individual during certain period of time.

$$C_v < \tilde{\lambda} \cdot C_i \tag{10}$$

$$\frac{C_i}{C_v} > \frac{1}{\tilde{\lambda}} \tag{11}$$

So, from social perspective vaccine costs must be less than:

$$C_v^{social} < PVB \cdot C_i \tag{12}$$

and from individual perspective:

$$C_v^{individual} < \tilde{\lambda} \cdot C_i \tag{13}$$

From formula (14) and (15) it can be easy to find subsidy level S as difference between optimal social and individual vaccine cost:

$$S = C_i^{social} - C_v^{individual} = \left[MB - \tilde{\lambda}\right] \cdot C_i \tag{14}$$

Next, a hypothetical VTG was considered, which is 12.5% (m) among the total susceptible synthetic population, and 67% (n) among all sick synthetic population, which roughly corresponded to children under 5 years old in Ukraine. The results of mathematical modeling of different levels of VTG possible rotavirus vaccine supply showed decrease of PVB and cumulative RVI probability with increase of VTG vaccine coverage (Fig. 5-6).

It allowed finding of potential optimal subsidy level as share of cost of illness with different levels of vaccine coverage. Its decrease was explained by potential epidemiological benefit of vaccination for nonvaccined individuals with vaccine coverage increase (Fig. 7).

CONCLUSIONS

Prediction of possible implications of RVI vaccination and finding optimal level of vaccine supply involves a comprehensive study of the epidemic process peculiarities of this infection with development of an adequate epidemiological model. We have proposed a model of RVI epidemiological process in Ukraine, determining its main parameters with the use of available retrospective data of anual number of RVI cases for the period from 2010 to 2016. The developed model was used as an analytical tool for analyzing influence of different levels of vaccine supply on vaccination cost-benefit. The results of research showed that the use of epidemiological modeling in pharmacoeconomic analysis of rotavirus vaccination made it possible to determine analytically optimal level of vaccination subsidy level.

REFERENCES

1. Pokrovskiy, V. I., Briko. N. I. Infektsionnyye bolezni v epokhu globalizatsii [Infectious diseases in the era of globalization]. Vestnik Rossiyskoy akademii meditsinskikh nauk, 2010; 11: 6-11.
2. Kawai K., O'Brien MA, Goveia MG et al. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. Vaccine, 2012; 30(7):1244-1254.
3. Tate JE, Burton AH, Boschi-Pinto C. et al. 2008 estimate of world wide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis., 2012; 12(2):136-41.
4. Sergevnin, V. I. Ostryye kishechnyye infektsii. Proyavleniya epidemicheskogo protsessa [Acute intestinal infections. Manifestations of the epidemic process]. Vrach, 2013; 9:18-20.
5. Shilov G.YU., Smirnova Ye.A. Analiz zabolevayemosti ostrymi kishechnymi infektsiyami v Rossiyskoy Federatsii, SSHA i stranakh Yevrosoyuza [Analysis of the incidence of acute intestinal infections in the Russian Federation, the United States and the European Union countries]. Pishchevaya promyshlennost'., 2013; 10:50–54
6. Lavronova E.S., Podkolzin A.T., Konovalova T.A. et al. Otsenka roli uslovno-patogennoy flory v razvitii ostrykh diareynykh zabolevaniy [Assessing the role of opportunistic flora in the development of acute diarrheal diseases]. Infektsionnyye bolezni, 2012; 10(3):53—55.
7. Lobzin YU.V. Klinika, epidemiologiya i profilaktika rotavirusnoy infektsii: metodicheskiye rekomendatsii [Clinic, epidemiology and prevention of rotavirus infection: methodical recommendations]. SPb.:NIIDI, 2013.
8. Dzyublik I., Nadraga O., Obertynska O., et al. Virus diseases of guts in children. Collection of scientific works of staff members of P.L. Shupyk NMAHE. – Kyiv (Ukraine), 2008; 17(2): 620–632.
9. Abaturov A.Ye. Podkhody k lecheniyu rotavirusnoy infektsii u detey [Approaches to the treatment of rotavirus infection in children]. Sovremennaya pediatriya, 2013; 1(49): 1–4.
10. Shalamay M. O., Storozhuk I. V. Osoblyvosti rotavirusnoyi infektsiyi u ditey molodshoho viku [Features of rotavirus infection in young children]. Biomedical and biosocial anthropology, 2014; 23: 132-135.
11. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet, 2016; 388:1459–1544.
12. Lanata CF, Fischer-Walker CL, Olascoaga AC, et al. Child Health Epidemiology Reference Group of the World Health Organization and UNICEF. Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. PloS One, 2013; 8:e72788.
13. Tate JE, Burton AH, Boschi-Pinto C, Parashar UD; World Health Organization–Coordinated Global Rotavirus Surveillance Network. Global, regional, and national estimates of rotavirus mortality in children <5 years of age, 2000–2013. Clin Infect Dis, 2016; 62(Suppl 2):S96–S105.
14. Wazny K., Zipursky A., Black R. et al. Setting Research Priorities to Reduce Mortality and Morbidity of Childhood Diarrhoeal Disease in the Next 15 Years. PLoS Med., 2013; 10(5):e1001446.
15. Kaira A.N., Solomay T.V. O vspyshke rotavirusnoy infektsii v mnogoprofil'nom statsionare [About the outbreak of rotavirus infection in a multidisciplinary hospital]. Sanitarnyy vrach, 2013; 8:35—38.
16. Hupperts H., Borte M., Schuster V. et al. Report of the Therd European Meeting on Rotavirus Vaccination: Progress in rotavirus universal mass vaccination in Europe. Vaccine, 2014; 32(34):4243-4248.
17. Cunliffe NA, Witte D, Ngwira BM, Todd S et al. Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life: a randomized, double-blind, placebo controlled trial. Vaccine, 2012; 30(Suppl 1):A36–A43
18. World Health Organization: Meeting of the immunization Strategic Advisory Group of Experts, April 2009–conclusions and recommendations. Wkly Epidemiol Rec., 2009; 84:220–236.

19. Cortese MM, Dahl RM, Curns AT, Parashar UD. Protection against gastroenteritis in US households with children who received rotavirus vaccine. J Infect Dis., 2015; 211(4):558–562.
20. Cherian T., Wang, S., Mantel C. Rotavirus vaccines in developing countries: the potential impact, implementation challenges, and remaining questions. Vaccine, 2012; 30(Suppl 1):A3–A6.
21. Vesikari T. Rotavirus vaccination: a concise review. Clin Microbiol Infect., 2012; 18(Suppl 5):57–63.
22. Steele AD, Neuzil KM, Cunliffe NA et al. Human rotavirus vaccine Rotarix provides protection against diverse circulating rotavirus strains in African infants: a randomized controlled trial. BMC Infect Dis., 2012; 12:213.
23. Dzyublyk I.V., Obertyns'ka O.V., Solovyov S.O., Trokhymenko O.P. Molekulyarno-biolohichni doslidzhennya ta prohnozuvannya henotyp spetsyfichnoyi efektyvnosti protyrotavirusnoyi vaktsyny na terytoriyi Ukrayiny [Molecular biological research and forecasting of the genotype of specific effectiveness of an antiviral vaccine in Ukraine]. Dovkillya ta zdorov'ya, 2011; 3:44-47.
24. Dietz K. Epidemics and Rumours: A Survey. Journal of the Royal Statistical Society, 1967; 130:505-528.
25. Kermack W.O., McKendrick A.G. A Contribution to the Mathematical Theory of Epidemics. Proceedings of the Royal Society of London, 1927; 115:700-721.
26. Anderson R. M., May R. M. Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford, United Kingdom, 1991.
27. Velázquez F. R. et al. Rotavirus Infection in Infants as Protection against Subsequent Infections. N Engl J Med., 1996; 335:1022-1028.
28. Ruuska T., Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. ScandJ. InfectDis., 1990; 22(3):259-267.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Serhii O. Soloviov
Department of virology of the
Shupyk National Medical Academy of Postgraduate Education
9 Dorohozhytska Str., Kyiv, 04112 Ukraine
tel: +380661566081
e-mail: solovyov.nmape@gmail.com

Received: 20.02.2019
Accepted: 17.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

INSTRUMENTAL ASSESSMENT OF MYOCARDIAL FUNCTION BY DOPPLER TISSUE IMAGING IN CHILDREN WITH CONGENITAL HEART DEFECTS AFTER SURGICAL CORRECTION AND ITS CORRELATION WITH GALECTIN-3 AMOUNT AS BIOLOGICAL MARKER OF CARDIAC FIBROSIS

Veronika Dudnyk[1], Olha Zborovska[1], Yuilia Vyzhga[1], Kateryna Khromykh[1], Ganna Zvenigorodska[1], Vladymyr Popov[1], Valentyn Bakhnivskyi[2,3]

[1]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSYA, UKRAINE
[2]CRACOW UNIVERSITY OF ECONOMICS, CRACOW, POLAND
[3]STEFAN ŻEROMSKI HOSPITAL IN CRACOW, CRACOW, POLAND

ABSTRACT

Introduction: Speed myocardial indicators and estimation of galectin-3 presented for estimation of myocardial dysfunction in children with congenital heart defects (CHD).

The aim: Evaluate myocardial function while using tissue Doppler imaging (TDI) and galectin-3 in children with CHD after surgical correction.

Materials and methods: We examined 184 children. The study assessed both ventricle systolic and diastolic performance by TDI in combination with tricuspid annular plane systolic excursion (TAPSE). Additionally, systolic (S') and diastolic (ratio E/E') TDI measurements were obtained at the lateral part of mitral annular, interventricular part, and lateral part of tricuspid valve (S`ma lateral, S` ma septal, S`ta lateral та E/E' malateral, E/E' maseptal, E/E' talateral). Galectin-3 amount in serum was detected by immune enzyme method by kit «HumanGalectin-3».

Results: Compared to results of the healthy children systolic TDI measurements in patients with CHD were significantly lower: S` ma lateral 7,81±0,10 cm/s vs 9,85±0,28 cm/s, S` ta lateral 9,70±0,12 cm/s vs 12,8±0,17 cm/s and TAPSE, 1,48±0,02 vs 2,14±0,03 cm/s ($p<0,01$). Ratio E/E' in patients with CHD were different from results of the healthy children in all myocardial segments: E/E` ma lateral 7,45±0,21 vs 6,17±0,12, E/E` ma septal 9,17±0,22 vs 7,54±0,13, E/E` ta lateral 6,42 ± 0,14 vs 4,64±0,12, ($p<0,05$). Patients with CHD got galectin-3 content in serum 7,04±0,21 ng/ml vs 4,17±0,17 ng/ml ($p<0,01$) results of the healthy children.

Conclusions: Analyze of TDI measurements and galectin-3 content allows evaluate myocardial dysfunction in asymptomatic patients with CHD after surgical correction.

KEY WORDS: congenital heart defects, children, myocardial dysfunction, tissue Doppler imaging, galectin-3

Wiad Lek 2019, 72, 7, 1281-1287

INTRODUCTION

Congenital heart defects (CHD) are still the most common abnormalities in children population, with the frequency up to 20 – 30 % through the all physical disabilities. Europe had the second highest reported total CHD birth prevalence (8.2 per 1,000 live births [95% CI: 8.1 to 8.3])[1]. For the past 2-3 decades new important changes in cardio surgery were done, that allows adequately correct most of the anatomical variants of CHD in time, as well influence enlargement of the patients amount after the surgical correction every year [2,3]. Prolonged clinical observance after such patients shows that more than half of them have residual pathology and need medical support, control and rehabilitation. It's known that for patients with cardiovascular pathology the most important sign of the consequences prognosis is development of the heart failure (HF). According to the last data reviews, patients with CHD have HF in 15-25 % [4], and amount of the kids with HF after the surgical correction of heart abnormalities is significantly higher – 61,4 % [5]. Adult population has HF traditionally associated with decreased contractility of left ventricle, that is evaluated by ejection fraction (EF). In pediatric population reasons of HF are different and mainly caused by involvement of the right ventricle (RV), that is common for CHD with left-right shunting and volume overloading of the right chambers and output obstruction of the RV [5]. Complicated geometry of the RV doesn't allow evaluate its function adequately during routine Echo-CG. Practical value of modern Echo-CG is dedicated to method of tissue Doppler imaging that allows estimate systolic and diastolic function of both left and right ventricles according to speed myocardial parameters. [6,7,8].

Fundamental data check presented important role of cascade activation of the biological markers, as result of the myocardial stress and cardiomyocytes damage, in pathogenesis of HF. Most of the known markers, as troponins, creatine phosphokinase in myocardial fraction, brain natriuretic peptide are the results of the pathological process,

but not a reason of the myocardial damage [9,10]. Due to all these reasons, role of the biological factors is intensively discussed, and their value for myocardial remodeling, dysfunction development has been predicted. Protein from the S-lectines galectin-3 is one of the most important predictors of myocardial remodeling, cause takes part in plural physiological and pathological processes, as inflammation, fibrosis that are reasonable and influence on development and progression of the pathophysiological mechanisms in HF [11]. Unlike most of the biological markers of HF, extracellular galectin-3 plays important role in cardio fibrotic processes and remodeling, though it's not a result, but a reason of the myocardial damage, so can be checked as perspective stream of the pathogenic therapy [12].

THE AIM

The goal of our study was to evaluate myocardial function of both ventricles with tissue Doppler imaging and its connection with fibrotic marker galectin-3 in children with CHD after surgical correction.

MATERIALS AND METHODS

We had checked 184 children (93 boys and 91 girls) with CHD that were provided with surgical correction of anatomical defects at the age between 1 month up to 18 years (average age was 9,54±0,36 years). According to hemodynamic type of disorder, all patients were divided on 3 groups: patients with CHD and enrichment of pulmonary circulation (PC) that presented by atrial and ventricle septal defects; patients with CHD and impoverishment of PC (Fallo tetralogy) and patients with CHD and impoverishment of systemic circulation (SC) (aorta coarctation and congenital aortal stenosis). Materials of the study presented according to bioethical norms of Helsinki declaration, adopted by General assembly of World medical convention, European council of the human rights and biomedicine (1977 p.).

For evaluation of the systolic and diastolic functions of the myocardium for all the patients Echo-CG was done on Philips HD11 XE, sensor from 3,5 to 7 MHz. Ultrasound scanning was done by TDI. For evaluation of systolic function of the LV we estimated peak systolic myocardial speed of the lateral part of mitral annular (S`ma lateral cm/s) and on the level of the basal part of the ventricle septum (S`ma septal cm/s). Contractility of the RV was estimated by identification of the tricuspid annular plane systolic excursion (TAPSE, cm), as well as systolic myocardial speed of the lateral part of tricuspid annular (S`ta lateral cm/s). Diastolic function of the LV was evaluated by integral E/E` ratio - the ratio of early transmitral blood flow velocity over tissue, Doppler early diastolic mitral annulus velocity (E/E`ma lateral and E/E`ma septal). The same index was calculated for RV at the level of tricuspid lateral part- E/E`ta lateral.

Amount of galectin-3 in serum was evaluated with immune enzyme method by «Human Galectin-3» (Platinum ELISA; eBioscience, BenderMedSystems, Austria) according to the product instructions. We divided amount of gelectin-3 according to statistical method for variation series on quartiles: I quartile – less than 5,62 ng/ml, II quartile – 5,62 – 6,21 ng/ml, III quartile – 6,22 – 7,73 ng/ml, IV quartile – more than 7,73 ng/ml.

The control group consisted of 40 age-matched healthy children.

Evaluation of the results: results were statistically proceeded with computer programs IBMSPSS Statistics, version 12 (20). All data were expressed as mean ±SD. Estimation of differences between average meanings was done by coefficient «t» to Students method, percentage values were detected by Fishers method. Approvement of the differences was counted by standard possibility (p) – $p<0,05$. For difference between comparative values was evaluated ratio of risks. Assessment of the degree of influence of factor characteristics was evaluated by odds ratio for 95%.

RESULTS

During evaluation of myocardial systolic function in patients with CHD TDIS`ma lateral was significantly lower to compare with healthy children – 7,81±0,10 cm/s vs 9,85±0,28 cm/s ($p<0,01$). While we analyzed correlation between S`ma lateral and hemodynamic type of CHD, was figured out that in case CHD with enrichment and impoverishment of the PC its meaning was in 1,20 and 1,25 times lower to compare with results of the healthy children. The highest differences in patients with CHD and impoverishment of the SC, that got S`ma lateral – 6,51±0,23 cm/s that was lower than result of the healthy kids in 1,51 times ($p<0,01$). The same tendency was occurred for S` ma septal (6,82±0,07 cm/s in CHD with enrichment of the PC, 5,96±0,23 cm/s in CHD with impoverishment of the PC and 6,13±0,10 cm/s in case of defects with impoverishment of the systemic circulation vs 7,93±0,13 cm/s in a group of healthy kids, $p<0,01$)(figure 1).

According to TD decreasing of the speed characteristics of RV cross contractility was observed in 133 (72,28±3,30 %) children. Though, S`ta lateral and TAPSE were decreased to 9,70±0,12 vs 12,8±0,17 cm/s and 1,48±0,02 vs 2,14±0,03 cm/s, that is 31,96 % and 44,59 % lower than healthy children's results. Analyze of the indicated characteristics in a correlation with type of CHD showed, that in CHD with septal defects TAPSE was significantly lower in 1,51 times (1,42 ± 0,02 cm, $p<0,01$), and S`ta lateral in 1,33 times (9,62±0, 11 cm/s, $p<0,01$) to compare with healthy children. At the same time, CHD with impoverishment of the pulmonary circulation got decreased TAPSE in 1,67 times (1,28±0,03 cm, $p<0,01$), and S`ta lateral in 1,59 times (8,04±0,19 cm/s, $p<0,01$) to compare with results of the healthy children and had significant difference with features of other types of CHD ($p<0,01$) (figure 2).

We figured out that CHD with impoverishment of systemic circulation had significantly lower peak systolic myocardial speeds of mitral annular: S` ma lateral<7,7 cm/s (OR=10,250; 95 % CI 2,984–35,211) and S` ma septal <6,5 cm/s (OR=6,324; 95 % CI 2,300–17,388). Residual output obstruction of RV in CHD with PC impoverishment followed by rising up of the chances of decreased systolic function of right chambers, with decreasing of the

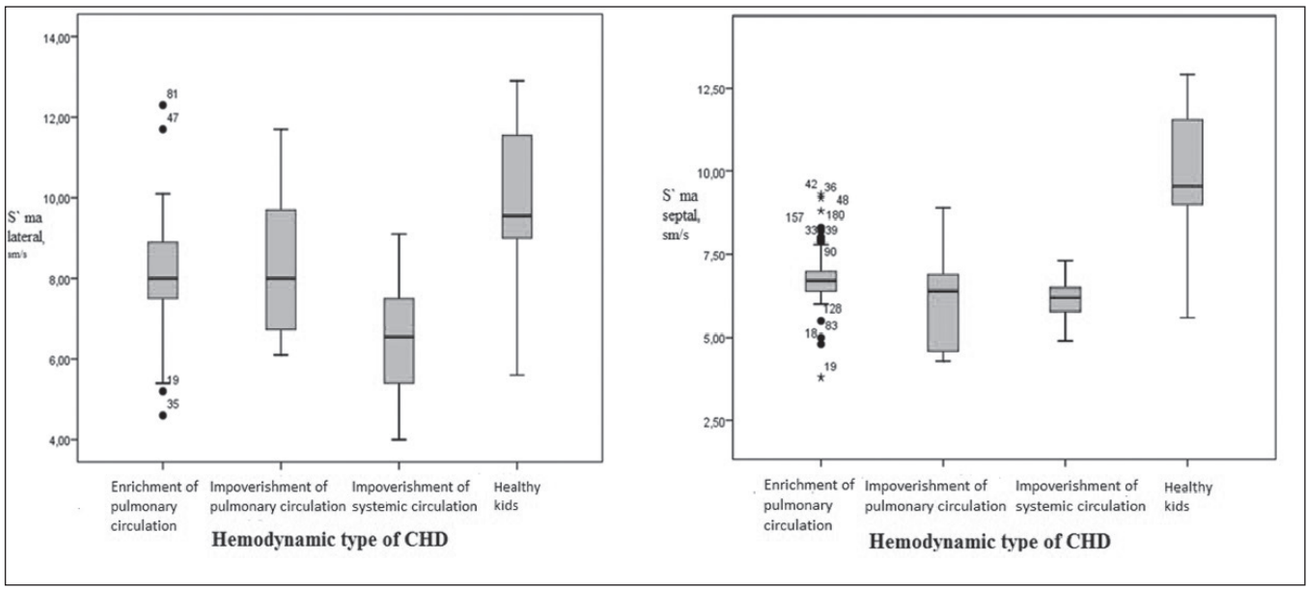


Fig. 1. Peak systolic myocardial velocities of the lateral part of mitral annular (S`ma lateral, cm/s) and on the level of the basal part of the ventricle septum (S` ma septal, cm/s) depending on the hemodynamic type of congenital heart disease.

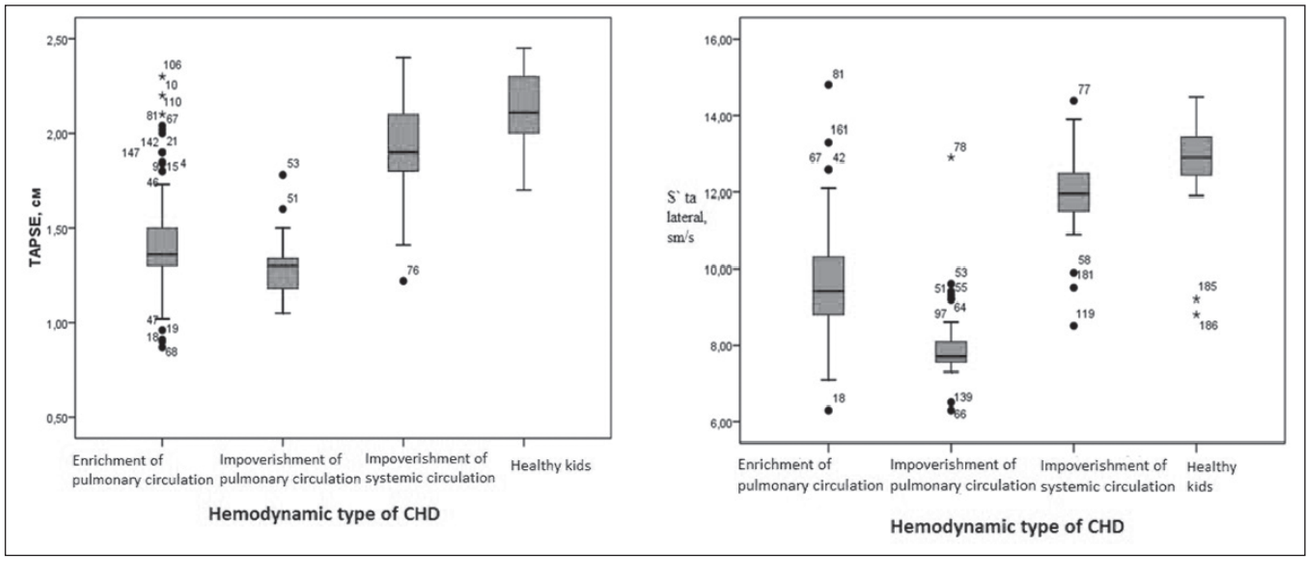


Fig. 2. Tricuspid annular plane systolic excursion (TAPSE, cm) and peak systolic myocardial velocities of the lateral part of tricuspid annular (S`ta lateral, cm/s) depending on the hemodynamic type of congenital heart disease.

amplitude of TAPSE<1,4 cm (OR=7,969; 95 % CI 2,929–21,678) and S` ta lateral <9,4 cm/s (OR=23,803; 95 % CI 5,505-102,923).

During evaluation of the diastolic myocardial function in children with CHD attitude E/E` was different from results of the healthy children in all myocardial segments: E/E`ma lateral 7,45±0,21 points vs 6,17±0,12(p<0,05) and E/E`ma septal 9,17±0,22 points vs 7,54±0,13(p<0,05), and E/E`ta lateral on 6,42 ± 0,14 points vs 4,64±0,12 (Table I).

Observation after the children with CHD with PC impoverishment after surgical correction follows by significant rising of a chance of relaxation disorders development in RV (for E/E`ta lateral>7,1points: OR=6,025; 95 % CI 2,738-13,257), and in case of CHD with systemic circulation impoverishment got significant risks of LV diastolic dysfunction (forE/E`ma lateral >7,5 points.: OR=18,714; 95 % CI 7,201-48,635).

All the patients were provided by evaluation of galectin-3 amount in serum. Patients with CHD got galectin-3 in serum 7,04±0,21 ng/ml vs 4,17±0,17 ng/ml (p<0,01) in a healthy children group. Analyze of its amount changes depending on hemodynamic type of CHD presented its reliable increasing in all types of CHD (p<0,01), especially those followed by SC impoverishment, that got its meaning higher results of the healthy children more than in 2 times (Table II).

We estimated TDI measurements in children with CHD depending on galectin-3 amount. While studying indicators of myocardial systolic function of both ventricles we

Table I. Peak-to-peak ratio of early diastolic filling of the ventricles (E/E`) depending on the hemodynamic type of congenital heart defect

E/E`ratio	CHD with enrichment of pulmonary circulation n=119	CHD with impoverishment of pulmonary circulation n=35	CHD with impoverishment of systemic circulation n=30	All patients with CHD n=184	Healthy children n=40
E/E`malateral	6,81±0,22*	6,83±0,21*	10,76±0,67*;**	7,45±0,21*	6,17±0,12
E/E` maseptal	8,63±0,29*	10,72±0,42*;**	9,51±0,34*	9,17±0,22*	7,54±0,13
E/E` talateral	6,22±0,16*	7,55±0,45*;**	5,90±0,19*	6,42±0,14*	4,64±0,12

Note: * - p<0,05–difference is trust worthy relatively to healthy children;
**- p<0,05 difference is trust worthy relatively to children with other CHD.

Table II. Concentration of galectin-3 in serum of the children surveyed

Meaning	CHD with pulmonary circulation enrichment n=119	CHD with pulmonary circulation impoverishment n=35	CHD with systemic circulation impoverishment n=30	All children CHD n=184	Healthy children n=40
Galectin-3, ng/ml	7,08±0,21*	5,69±0,27*	8,42±0,86*;**	7,04±0,21*	4,17±0,17

Note: *– p<0,01 – difference is trustworthy relatively to healthy children;
** – p<0,01 – difference is trust worthy relatively to children with CHD pulmonary circulation impoverishment.

found that in patients with CHD had trustworthy decreasing of the myocardial contractility of both right and left ventricles relatively to healthy children in all galectin-3 quartiles. At the same time significant difference in a speed systolic features with presented quartiles of galectin-3 were not detected (Table III).

Our analysis of E/E` ratio in children with CHD in different myocardial segments depending on galectin-3 content showed that meaning of E/E`ma lateral ratio progressively increased in patients with rising up of the galectin-3 content in serum but was trustworthy related just in 4 quartile (8,58±0,55 vs 6,34±0,25, p<0,05). Interquartile distribution of E/E`ma septal ratio showed the same tendency of its content increasing in serum, but trustworthy enlargement of E/E` ma septal ratio was observed just in 4 quartile of galectin-3 (9,61±0,35 vs 8,60±0,24, p<0,05). Interquartile distribution of diastolic peaks at the level of lateral tricuspid part didn't find trustworthy difference between E/E`ta lateral and galectin-3 content in serum (Table IV).

In the study of galectin-3 as prognostic marker of relaxation disorders we found trustworthy increasing of E/E` ma lateral ratio> 7,5points in galectin-3 content in serum - 6,21 ng/ml (OR=2,643; 95 % CI 1,297-5,384).

DISCUSSION

For kids after surgical correction of CHD common to receive residual pathology that influence on preload and afterload of ventricles that can lead to development of myocardial dysfunction. Most of the kids after surgical correction for a long period of time staying asymptomatically that is why search of the instrumental or biochemical markers of HF allows provide in time medical intervention.

For routine examination of myocardial function method of EchoCG is wide used. But, if LV is available for examination during regular scanning, RV due to complicated geometry can't be visualized adequately while using traditional Echo-CG [8]. RV has pronounced trabecularity that complicate estimation of its borders, as for some calculations we need exact myocardial borders. As well, muscle fibers of RV located mainly in longitudinal position, so most of the constrictions are hold in a such plane, in opposite towards oblique, longitudinal or circular myofibers [6,8].That is why adequate estimation of myocardial function, especially of the RV, can be hold just in case of use methods, that characterize work of the longitudinal fibres. One of such known methods is TDI. Tissue Doppler systolic velocity of the tricuspid annular is common for routine practice and easy in calculations with normal reference values available for the paediatric population [13]. Saxena N and others showed that S` talateral > 10,5 cm/s is associated with adequate function of RV and normal pressure in pulmonary artery [14].In other study was presented that systolic tricuspid annular velocity < 11.5 cm is associated with EFRV< 45 % with 90% sensitivity and 85% specification [15]. Most of the studies that explored RV function in children after surgical correction of CHD is dedicated to patients with tetrad of Fallot [16]. At the study of 183 children with tetrad of FallotS` on tricuspid valve was compared with EF of RV and final-diastolic volume index of RV estimated by magnetic resonance imaging (MRI). Results of the study showed that S` positively correlated with EF of RV (r = 0,66, P <0,001) and S` negatively correlated with final-diastolic volume index of RV (r = -0,59, P <0,001), that allows to use TDI as noninvasive method for RV examination without additional radiological influence[17].

Table III. Galectin-3 content depending on echocardio indicators of myocardial systolic function of both ventricles

Indicator	Galectin-3				P value
	1 quartile (< 5,62 ng/ml) n=45	2 quartile (5,62-6,21 ng/ml) n=48	3 quartile (6,22-7,73 ng/ml) n=45	4 quartile (>7,73 ng/ml) n=46	
S`malateral, cm/s	8,28±0,23	7,61±0,17	7,56±0,21	7,80±0,18	NS
S` maseptal, cm/s	6,36±0,18	6,55±0,12	6,71±0,15	6,56±0,09	NS
TAPSE, cm	1,36±0,04	1,39±0,04	1,63±0,05	1,53±0,04	NS
S` talateral, cm/s	9,36±0,29	9,49±0,21	10,04±0,28	9,91±0,20	NS

Note: NS, not significant

Table IV. Ratio of early diastolic filling of the ventricles (E/E`) in children with CHD depending on galectin-3 content

Ratio	Galectin-3				P value
	1 quartile (< 5,62 ng/ml) n=45	2 quartile (5,62-6,21ng/ml) n=48	3quartile (6,22-7,73ng/ml) n=45	4 quartile (>7,73ng/ml) n=46	
E/E` ma lateral, points.	6,34±0,25	7,25±0,38	7,63±0,39	8,58±0,55*	p<0,05
E/E`ma septal, points.	8,60±0,24	9,12±0,46	9,36±0,50	9,61±0,35*	p<0,05
E/E` talateral, points.	6,24±0,27	6,32±0,22	6,43±0,32	6,70±0,33	NS

Note: * – p<0,05 – difference is trustworthy on 1 quartile results of galectin-3. NS, not significant

E/E` ratio is integral marker increasing of it displays ventricle filling pressure rising. NORRE study, in 2015 presented data from adults for RV, and normal value is used to be ratio E/E`<15 [18]. Another data of 24 studies where ratio E/E` and left ventricular filling pressure were compared by invasive method, showed insufficient sensitivity of the method: 64 % for E/E` ma lateral and 50 % for E/E`ma septal, that needs further evaluation in prospective studies [19].

In our study with TDI we were able to find changes of the speed indicators during systole in 133 (72,28±3,30 %) children with relaxation disorders in 91 (49,46±3,69 %) persons.We want to admit, that all kids were clinically asymptomatic and after surgical correction of anatomical defects in different variants of CHD. As well, S`ma lateral, S` ma septal, S` ta lateral were trustworthy lower in all types of CHD to compare with the same results of the healthy children. TAPSE was significantly lower the results of the healthy children, even in cases, when RV wasn't the main problem of the correction (aorta coarctation, aortal valve stenosis). Analyze of the relaxation characteristics of the myocardium by E/E` ratio showed that in CHD with pulmonary circulation impoverishment after surgical correction in 6 times increase chances of the diastolic RV dysfunction development and enlargement of E/E` ta lateral >7,1points. In case of CHD with systemic circulation impoverishment in 18 times raised chances of the LV diastolic dysfunction (E/E` ma lateral >7,5 points), that displays insufficient tolerance of the ventricles towards resistance overload due to residual gradients and pathways of outflow.

Fundamental studies show significant role of biological substances cascade in pathogenesis of HF, that can be used for diagnostic, prognosis and estimation of treatment efficacy reasons [20]. Galectin-3 has an important impact in myocardial remodeling processes, cause it's an element of plural physiological processes, such as inflammation and fibrosis, that leads to progression of path physiological mechanisms of HF. Galectin-3 influence macrophage migration, fibroblasts proliferation, collagen synthesis of the I type in cardiomyocytes [21, 12].One of the first who estimated role of galectin-3 was Sharma U. And others who estimated gene in severe arterial hypertension with myocardial involevement in experiment. Galectin-3 was one of the most severe regulated genes, which expression in decompensate heart was increased more than in 5 times [22].In 2011-2013 Baggen V and others examined 602 adults with CHD. Galectin-3 positively correlated with age, NYHA class, loss of sinus rhythm, cardiac dysfunction and NT-pro BNP[23]. While analyze studies dedicated to galectin-3 with CHD that are in Pubmed base for the last 10 years, most of them belong to adult population and analyze correlation of marker with frequency of hospitalization, mortality rate, glomerular filtration rate, severity of HF.One of the most full studies in pediatric population by Kotby A and others that studied galectin-3 in chronic HF with normal and decreased EF in 45 patients. Results showed that serum galectin-3 was significantly increased to compare with control (p> 0,001). Children with normally saved EF had higher results of galectin-3 neither patients with decreased contractility, but without statistically meaningful difference (p = 0,194). Levels of galectin-3 positively correlated with Ross classification of HF (p = 0,01) and E/E`ratio for mitral valve (p = 0,032) and negatively correlated with EF, S` and E`/A` according to TDI(p = 0,028, 0,022, 0,043). Galectin-3 was decreased

in patients who received spironolactone, as symptomatic treatment component (p = 0,049)[24].

According to our study content of galectin-3 in children with CHD significantly differed from results of the healthy children in case of all hemodynamic variants of the defects (p<0,01), at the same time all the kids were symptomless and with saved EF of LV (64,90±0,42 %). Patients that got galectin-3 closer to upper quartile (>7,73 ng/ml) in 5,3 times more frequent associated with period after the surgical correction of CHD more than 5 years (95 % CI 2,420-11,484), that presents humoral mechanisms of myocardial dysfunction progression in a postoperative catamnesis and influence residual pathology. We didn't find any statistically important connection between galectin-3 and decreasing of speed systolic markers of both ventricles. Analyze of E/E` ratio in children with CHD in different myocardial segments depending on galectin-3 found that meanings of ratio E/E` malateraland E/E` ma septal progressively increased with enlargement of marker in serum, but was important just at the level of 4$^{th}$ quartile of galectin-3 (>7,73ng/mlp<0,05). E/E` ta lateral ratio didn't demonstrate the same connection, even though ratio was different in healthy children at the level of all quartiles.

Study limitations: We didn't compare myocardial speeds got by TDI with parameters of invasive methods (MRI, chambercatheterization) in our study, because these investigations were not detected for our patients, due to absence of clinical signs of HF. We didn't achieve results about galectin-3 changes and potential improvement of functional myocardial condition at the background of the treatment.

CONCLUSION

Speed indicators of the myocardial function estimated by TDI allow provide qualities characteristics of both ventricles longitudinal contractility in different phases of myocardial cycle without clinical manifestation of HF. Connection of galectin-3 content and worsening of relaxation confirm its biological role in path physiological mechanisms of myocardial dysfunction development.

REFERENCES

1. Dolk H, Loane M, Garne Eet al. Congenital heart defects in Europe: prevalence and perinatal mortality 2000 to 2005.Circulation.2011; 123(8):841-849,doi: 10.1161/CIRCULATIONAHA.110.958405
2. Oster M, Lee K, Honein M et al. Temporal trends in survival among infants with critical congenital heart defects. Pediatrics.2013;131(5):1502–1508, doi: 10.1542/peds.2012-3435.
3. Razzaghi H, Oster M, Reefhuis J Long Term Outcomes in Children with Congenital Heart Disease: National Health Interview Survey. J Pediatr. 2015; 166(1): 119–124,doi:10.1016/j.jpeds.2014.09.006
4. Kay J, Colan S, Graham T Congestive heart failure in pediatric patients. Am Heart J. 2001; 142(5): 923-928, doi:10.1067/mhj.2001.119423
5. Beggs S, Tompson A, Nash R et al Cardiac failure in children in Proceedings of the 17th Expert Committee on the Selection and Use of Essential Medicines, World Health Organization, Geneva, Switzerland, March 2009, http://www.who.int/selection medicines/committees/expert/17/ application/paediatric/Paed Cardiac Failure Review.pdf
6. Di Lorenzo M, Bhatt S, Mercer-Rosa L How best to assess right ventricular function by echocardiography. CardiolYoung. 2015; 25(8): 1473–1481. doi:10.1017/S1047951115002255
7. GrohG, LevyP, Holland M et al Doppler Echocardiography Inaccurately Estimates Right ventricular Pressure in Children with Elevated Right Heart Pressure. J. Am. Soc. Echocardiogr. 2014; 27 (2): 163-171, doi: 10.1016/j.echo.2013.09.016
8. Ho S, Nihoyannopoulos P Anatomy, echocardiography, and normal right ventricular dimensions. Heart.2006;92(1):2–13, doi10.1136/hrt.2005.077875
9. BraunwaldE Biomarkers in heart failure. N Engl J Med. 2008; 358(20): 2148-2159, doi: 10.1056/NEJMra0800239
10. Sugimoto M, Kuwata S, Kurishima C,et al Cardiac biomarkers in children with congenital heart disease. World J Pediatr. 2015; 11(4): 309-15, doi: 10.1007/s12519-015-0039-x.
11. Morrow D, O'Donoghue M Galectin-3 in cardiovascular disease: a possible window into early myocardial fibrosis. J Am CollCardiol. 2012; 60(14): 1257-1258,.doi: 10.1016/j.jacc.2012.05.032
12. Ho J, Liu C, Lyass A, et al Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. J AmCollCardiol.2012; 60(14):1249-1256,doi: 10.1016/j.jacc.2012.04.053
13. Koestenberger M, Nagel B, Ravekes W, et al. Reference values of tricuspid annular peak systolic velocity in healthy pediatric patients, calculation of z score, and comparison to tricuspid annular plane systolic excursion. Am J Cardiol.2012;109(1): 116-121,doi: 10.1016/j.amjcard.2011.08.013
14. Saxena N, Rajagopalan N, Edelman K, et al. Tricuspid annular systolic velocity: a useful measurement in determining right ventricular systolic function regardless of pulmonary artery pressures. Echocardiography.2006;23(9): 750-755, doi.org/10.1111/j.1540-8175.2006.00305.x
15. Meluzin J, Spinarova L, Bakala J, et al. Pulsed Doppler tissue imaging of the velocity of tricuspid annular systolic motion; a new, rapid, and non-invasive method of evaluating right ventricular systolic function. EurHeart J.2001;22(4): 340-348, doi:10.1053/euhj.2000.2296
16. Villafañe J, Feinstein J, Jenkins K, et al. Hot topics in tetralogy of Fallot. J Am CollCardiol.2013;62(23):2155-2166,doi: 10.1016/j.jacc.2013.07.100
17. Koestenberger M, Nagel B, Ravekes W, et al. Tricuspid annular peasystolic velocity (S) in children and young adults with pulmonary artery hypertension secondary to congenital heart diseases and in those with repaired tetralogy of Fallot: echocardiography and MRI data. J AmSocEchocardiogr. 2012;25(10):1041–1049, doi: 10.1016/j.echo.2012.06.004
18. Caballero L, Kou S, Dulgheru R, et al. Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study. EurHeart J CardiovascImaging.2015;16(9): 1031-1041, doi: 10.1093/ehjci/jev083
19. Sharifov O, Schiros C, Aban I,et al. Diagnostic Accuracy of Tissue Doppler Index E/e' for Evaluating Left Ventricular Filling Pressure and Diastolic Dysfunction/Heart Failure With Preserved Ejection Fraction: A Systematic Review and Meta-Analysis. J AmHeartAssoc.2016; 5(1): 1-19, doi: 10.1161/JAHA.115.002530.
20. Richards M Biomarkers and Silent Cardiac Disease in Primary Prevention Time to Unmask the Damage? Journal of the American CollCardiol. 2012; Vol. 60(11): 969-970, doi: 10.1016/j.jacc.2012.05.030
21. De Filippi C, Felker MGalectin-3 in Heart Failure – Linking Fibrosis, Remodelling and Progression.EurCardiol. 2010; 6(2): 33-36, doi: 10.15420/ecr.2010.6.2.33
22. Sharma U, Pokharel S, van Brakel T, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation. 2004; 110(19): 3121-3128, doi: 10.1161/01.CIR.0000147181.65298.4D

23. Baggen V, van den Bosch A, Eindhoven J, et al. Prognostic value of galectin-3 in adults with congenital heart disease. Heart. 2018; 104(5):394-400, doi: 10.1136/heartjnl-2017-312070
24. Kotby A, Youssef O, Elmaraghy M, et al. Galectin-3 in Children with Chronic Heart Failure with Normal and Reduced Ejection Fraction: Relationship to Disease SeverityPediatrCardiol.2017; 38(1):95-102. doi: 10.1007/s00246-016-1488-2

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Valentyn Bakhnivskyi
Stefan Żeromski Hospital in Cracow,
Cracow University of Economics
tel: +48576588771
mail: valentyn.bakhnivskyi@poczta.pl

Received: 12.02.2019
Accepted: 04.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

ASSESSMENT OF CHANGES OF SKIN MOISTURE IN PATIENTS SUBJECT TO GENERAL ANESTHESIA WITH NEUROLOGICAL DISEASES IN AN INTERVIEW

OCENA ZMIAN WILGOTNOŚCI SKÓRY U PACJENTÓW ZE SCHORZENIAMI NEUROLOGICZNYMI W WYWIADZIE, PODDANYCH ZNIECZULENIU OGÓLNEMU

Jolanta Piskorz[1], Gustaw Wójcik[2,3], Włodzimierz Bulikowski[4], Dorota Kozak-Putowska
[1]ZOFIA FROM ZAMOYSKI TARNOWSKA PROVINCIAL HOSPITAL IN TARNOBRZEG, TARNOBRZEG, POLAND
[2]DEPARTMENT OF REHABILITATION, PHYSIOTHERAPY AND BALNEOTHERAPY AT THE MEDICAL UNIVERSITY OF LUBLIN, LUBLIN, POLAND
[3]POPE JOHN PAUL II STATE SCHOOL OF HIGHER EDUCATION IN BIAŁA PODLASKA, BIALA PODLASKA, POLAND
[4]CENTRE OF OCCUPATIONAL MEDICINE IN GNIEZNO, GNIEZNO, POLAND

ABSTRACT

Introduction: General anaesthesia is carried out using anaesthetic agents that among others depress the circulatory system and CNS. Central and peripheral thermoregulation occurs, which is due to mild hypothermia as well as changes in skin moisture.

An important element of therapy in the perioperative period is adequate intravenous fluid therapy, which affects the final effects of treatment.

The aim: Evaluation of skin moisture as a result of changes in central and peripheral thermoregulation during general anaesthesia and evaluation of the hydration status of patients.

Material and methods: The study included 180 patients undergoing general anaesthesia for elective surgery, aged 20-85 years of age. Before general anaesthesia, patients were evaluated for ASA-related risk of anaesthesia (ASA 1 - healthy patients, ASA 2 and 3 - patients with neurological and circulatory disorders). Patients were divided into 2 groups, the study group (90 people) were patients who were given no intravenous fluids before the surgery and the control group (90 patients) were those receiving doses of 500 ml crystalline intravenously one hour before anaesthesia. The research was carried out at the Operational Block of the Provincial Hospital in Tarnobrzeg, from November 2013 to November 2014.

Skin moisture was measured using a CM 825 Corneometer: before general anaesthesia, after induction for anaesthesia, 15 min after surgical incision of the skin and after awakening the patient.

Results: Both in the test and control groups, statistically significant differences were found in subsequent skin moisture measurements. Pairwise comparisons indicate statistically significant differences between each pair of measurements. In both groups of patients, there is a clear decrease in skin moisture after induction of anaesthesia compared to the measurement performed before general anaesthesia. The skin moisture values are reduced in subsequent measurements, however the difference is much lower.

Conclusions:

1 Measurement of skin moisture can be used as one of the parameters to assess perioperative stress and changes in body temperature during general anaesthesia, which indirectly determines the functioning of the hypothalamus.

2 By measuring the skin moisture it is possible to indirectly assess the hydration status of patients as well as the decrease of the metabolism during general anaesthesia.

3 The decrease in skin moisture during general anaesthesia is the effect of changes in central and peripheral thermoregulation.

KEY WORDS: general anesthesia, CNS, skin moisture, hydration

STRESZCZENIE

Wstęp: Znieczulenie ogólne przeprowadzane jest za pomocą środków anestetycznych, które wpływają negatywnie m.in. na układ krążenia oraz OUN. Dochodzi do zaburzenia termoregulacji ośrodkowej i obwodowej, czego implikacją jest łagodna hipotermia, jak również zmiany wilgotności skóry. Istotnym elementem terapii w okresie okołooperacyjnym jest odpowiednia płynoterapia dożylna, która wpływa na końcowe efekty leczenia.

Cel pracy: Ocena wilgotności skóry jako efekt zmian termoregulacji ośrodkowej i obwodowej podczas znieczulenia ogólnego oraz pośrednio ocena stanu nawodnienia pacjentów.

Materiał i metody: Badaniami objęto 180 pacjentów poddanych znieczuleniu ogólnemu do planowych zabiegów operacyjnych, których wiek mieścił się w przedziale 20—85 lat. Przed znieczuleniem ogólnym pacjentów oceniano pod względem ryzyka związanego ze znieczuleniem według klasyfikacji ASA (ASA 1 – zdrowi pacjenci, ASA 2 i 3 – pacjenci obciążeni schorzeniami neurologicznymi i krążeniowymi). Pacjentów podzielono na 2 grupy: grupa badana (90 osób) to pacjenci, u których przed planowanym zabiegiem nie stosowano podaży dożylnej płynów i grupa kontrolna (90 osób), to chorzy otrzymujący dożylnie na godzinę przed znieczuleniem 500 ml krystaloidów. Badania wykonywano na Bloku Operacyjnym Szpitala Wojewódzkiego w Tarnobrzegu. Trwały od listopada 2013 roku do listopada 2014 roku. Wilgotność skóry mierzono przy użyciu Corneometru CM 825: przed znieczuleniem ogólnym, po indukcji do znieczulenia, 15 minut po nacięciu chirurgicznym skóry oraz po wybudzeniu pacjenta.

Wyniki: Zarówno w grupie badanej, jak i kontrolnej odnotowano istotne statystycznie różnice w kolejnych pomiarach wilgotności skóry. Porównania parami wskazują na istotne statystycznie różnice pomiędzy każdą parą pomiarów. W obu grupach pacjentów widoczny jest wyraźny spadek wilgotności skóry po indukcji znieczulenia w porównaniu do pomiaru wykonanego przed znieczuleniem ogólnym. Wartości wilgotność skóry ulegają obniżeniu w kolejnych pomiarach, jednak różnica jest już znacznie mniejsza.

Wnioski:

1. Pomiar wilgotności skóry może posłużyć jako jeden z parametrów do oceny stresu okołooperacyjnego i zmian temperatury ciała podczas znieczulenia ogólnego, co w sposób pośredni określa funkcjonowanie podwzgórza.
2. Poprzez pomiar wilgotności skóry można ocenić pośrednio stan nawodnienia pacjentów oraz spadek metabolizmu podczas znieczulenia ogólnego.
3. Spadek wilgotności skóry podczas znieczulenia ogólnego jest efektem zmian termoregulacji ośrodkowej i obwodowej.

SŁOWA KLUCZOWE: znieczulenie ogólne, OUN, wilgotność skóry, nawodnienie

Wiad Lek 2019, 72, 7, 1288-1294

INTRODUCTION

The purpose of general anaesthesia is to guarantee amnesia, analgesia and optimal surgical conditions while ensuring patient's safety. The basis of general anaesthesia is intentional and reversible limitation of the central nervous system (CNS), which is achieved at the expense of depression of all functions of the undamaged nervous system.

The nervous system is the place of action of anaesthetics, which is associated with the weakening or abolition of CNS defence mechanisms [1]. Therefore, intra-operative blood pressure fluctuations, blood volume deficiencies, ventilation disorders, disturbances of acid-base and water-electrolyte balance have more damaging effects than in the conscious patient, whose functional nervous system enables the inclusion of compensatory mechanisms. The mentioned mechanisms are aimed at maintaining a safe energy level of every cell of the living organism [2].

CNS status is very important in the period preceding surgery and general anaesthesia, because diseases or situations leading to increased energy consumption or limiting the inflow of energy substrates to the brain or spinal cord lead to postoperative complications. Increased energy consumption occurs in case of seizures or epileptic states, also strong emotional reactions cause a rapid increase in brain metabolism and rapid depletion of energy reserves. Damage to the blood-brain barrier, the use of substances that stimulate the activity of CNS cells, or feverish states contribute to the increased energy consumption of brain cells [2].

The inhalational anaesthetics used in general anaesthetics, hypnotic agents, neuromuscular blockers, opioid analgesics, as well as atropine and polymigmine exert a differential effect on cerebral function. The amount of blood flow (CBF) through the CNS and its intracranial pressure (ICP) correlated with it may change during general anaesthesia caused by direct action of anaesthetics on the walls of blood vessels or by their effect on blood flow regulating systems.

The introduction of the patient into the state of general anaesthesia also causes changes in thermoregulation consisting in the tenfold increase in the range of the allowable target temperature in the hypothalamus. Most anaesthetics lower the basic level of metabolism, they also work peripherally causing diastolic vasodilation, which results in the development of mild hypothermia during surgery. During the first hour of anaesthesia, the internal temperature drops by 1 ° C (phase 1). A further decrease in temperature to 34-35 ° C (phase 2) occurs for the next three hours of anaesthesia. After this period, a new balance is established between production and peripheral heat loss (plateau phase - 3) [3].

It should be noted that exceeding the thermoregulatory capabilities of the body in extreme thermal conditions of the environment or in the case of impairment of the body temperature regulation mechanism leads to hypothermia or hyperthermia, which can lead to death.

One of the methods used to assess body thermoregulation is the measurement of skin moisture, because sweat glands are an important effector of physical thermoregulation in humans. The activity of the sweat glands is stimulated by impulses reaching the cholinergic sympathetic fibres. Activation of these glands occurs under the influence of stimulation of thermo-detector centres sensitive to the increase of the internal temperature, where there is a direct relationship between the amount of secreted sweat and the temperature of blood flowing into the hypothalamus.

In the regulation of body temperature, the subcutaneous venous plexus, supplied with blood from the skin capillaries, is very important. The volume of blood flowing through the venous plexus varies from 0-30% of the heart's capacity. Enlargement of the blood vessels of the skin increases the flow of blood, causing the increase of heat elimination from the inside of the body to its surface [4].

The use of appropriate fluid therapy (fluid osmolarity and quantity) is essential for the functioning of the CNS. Dangerous complication resulting from intraoperative hypovolaemia are transient disturbances of CNS perfusion and oxygenation. A prolonged decrease in oxygenation of the brain tissue leads to ischemia within the CNS or cerebral infarction, which may be limited to a small focus of dysfunction or stroke. In patients with atherosclerosis, and especially with cerebrovascular disease, there is an increased risk of ischemic brain damage associated with hypotension due to hypovolaemia and the use of anaesthetic agents [5].

THE AIM

Evaluation of skin moisture as a result of changes in central and peripheral thermoregulation during general anaesthesia and indirect assessment of patient hydration status.

Table I. Test groups divided into gender and treatment unit

Gender – n (%)	Men	43 (47.78%)	43 (47.78%)	Chi^2=0.022 df=1 p=0.881
	Women	47 (52.22%)	47 (52.22%)	
Hospital unit – n (%)	General surgery	40 (44.44%)	42 (46.67%)	Chi^2=0.132 df=2 p=0.936
	Gynaecology	25 (27.78%)	23 (25.56%)	
	Laryngology	25 (27.78%)	25 (27.78%)	
In total		90	90	

Table II. The age of the subjects

Group of patients	Age of subjects				
	Average	Median	Minimum	Maximum	SD
Study group	51.96	52.0	20.0	81.0	16.16
Control group	51.99	50.5	20.0	85.0	15.24

MATERIAL AND METHODS

The research was carried out on a group of 180 patients (the study group of 90 patients, the control group of 90 patients), the age of the respondents ranged from 20 to 85 years of age. The patients were subjected to general anaesthesia for planned surgical operations taking place at the Operational Block in the Provincial Hospital in Tarnobrzeg. The research was conducted from November 2013 to the end of November 2014.

The surveyed patients were hospitalized in the departments of general surgery, gynaecology and laryngology. The examined group from the department of general surgery consisted of 40 patients, which represents 44.40% of examined patients, in the control group there were 42 people (46.67%). From the department of gynaecology in the examined group there were 25 patients (27.78%), in the control group of this department there were 23 patients (25.56%). In the laryngology department 25 patients were included in the study (27.78%), in the control group 25 patients were also examined (27.75%).

In the study group the number of women was 52.22% (47 people), and men 47.78% (43 people). Analogously the number of women and men in the control group was 52.22% 47.78% (Table I).

The average age of patients in both the test and control groups was comparable - in the study group it was 51.96, in the control group 51.99 (Table II).

All patients were evaluated for the risk associated with general anaesthesia according to the ASA classification (American Anaesthesiological Society). A comparable number of healthy (ASA 1) and disease-burdened patients (ASA 2 and ASA 3 - an increased risk related to anaesthesia and surgery) was selected. Patients with ASA 2 and 3 are patients who have had history of ischemic stroke, TIA (transient cerebral ischaemia), are currently suffering from epilepsy, Parkinson's disease, diabetic polyneuropathy, or have cerebrovascular atherosclerosis confirmed by imaging (Table III).

All patients on the day of planned surgery maintained a nutritional grace period of at least 6 hours before the planned general anaesthesia. 40 minutes before general anaesthesia, they received premedication in the form of 7.5 mg dormicum orally.

The study included patients with normal body temperature before general anaesthesia. The control group consisted of patients receiving intravenously 500 ml crystalloids an hour before general anaesthesia. Skin moisture tests were conducted on those patients whose general anaesthesia lasted an average of 60-90 minutes. The study included patients who had expressed their informed written consent, after having read the protocol of the tests.

The approval of the Bioethics Committee of the Medical University in Lublin with the number KE - 0254/257/2013 was obtained for the above tests.

Methods of work:

Skin moisture measurements were made:

- before general anaesthesia,
- after induction for anaesthesia and intubation of the patient,
- fifteen minutes from the start of the procedure,
- after waking up and extubating of the patient

Skin moisture measurements were made using the Corneometr CM 825 from Courage - Khazaka (Köln, Germany), which was connected to the MPA 580 Cutometer. The tests were performed on the inside of the forearm in the middle part and on the fingertip of the fifth finger. This limb was uncovered during the entire duration of anaesthesia, and infusion fluids were not infused through the veins on the examined limb. The upper limb, on which the measurements were made, was placed on a special support and situated sideways. The skin before the examination was washed with an disinfectant (skinsept pur), and then dried. Skin moisture measurements were not made on the scalp to eliminate unreliable results.

Skin moisture was measured using a CM 825 Corneometer probe, which was placed vertically in the area of the skin to be examined. The probe started the measurement at the moment of contact with the skin, the sound signal meant successful measurement. The average value of both measurements (fore-

Table III. The division of patients due to the classification of ASA.

ASA		Study group n (%)	Control group n (%)	Chi²
ASA	ASA 1	49 (54.44%)	47 (52.22%)	Chi²=0.022 df=1 p=0.881
	ASA 2–3	41 (45.56%)	43 (47.78%)	
In total		90	90	

Table IV. Change in skin moisture during general anaesthesia

Skin moisture	M	SD	Analysis of variance	Pair comparisons *
			Study group	
I. before anaesthesia	59.10	11.48	F (2,12, 188,44) = 288,38 p<0.001 *eta²=0.764*	I-II, I-III, I-IV, II-III, II-IV III-IV
II. after induction for anaesthesia	45.69	10.10		
III. minutes after skin incision	38.98	8.04		
IV. after waking up	33.63	7.38		
			Control group	
I. before anaesthesia,	64.38	9.98	F (2,06, 183,08) = 666,95 p<0.001 *eta²=0.882*	I-II, I-III, I-IV, II-III, II-IV III-IV
II. after induction for anaesthesia	49.77	7.98		
III. minutes after skin incision	41.75	6.61		
IV. after waking up	37.15	5.22		

arm and fifth fingertip) was displayed and recorded using numerical values and bar charts along with data on temperature and humidity in the operating room. The measurement time with the Corneometer probe was about 1 second.

Operating theatres where skin moisture measurements were carried out were air-conditioned and maintained a temperature of 22 ° C and a relative humidity of 40%.

Skin moisture measurements using the CM 825 Corneometer are based on the capacitive method. The results of corneometric measurements are given in arbitrarily accepted units ranging from 0 to 130j. The interpretation is as follows: if the measurement value is below 30 units, it means very dry skin, dry skin - 30 to 45 units, and skin sufficiently moisturized above 45 units.

The crystalloid infusions of 15-20 ml / kg mc / h were used in the studied patients including intraoperative blood and fluid loss. Ringer's solution and Sterofundin were most commonly used, in patients with diabetes, KIG was used as an additional fluid (10 Glucose, 8 units of insulin, 40mEq KCl). Colloids were received by patients who had severe hypovolaemia during the procedure.

The following tests were used to perform the statistical analysis:

1. Analysis of ANOVA variance for dependent samples - changes in skin moisture were assessed at individual stages of the study between the test and control groups.

2. Correlation of r-Pearson, where correlations of skin moisture were assessed with the age of patients included in the study.

3. Student's t-test for independent tests, where skin moisture was compared in patients at individual stages of the study and skin moisture between ASA1 patient and ASA2 and 3 patients.

RESULTS

Table IV presents the results of changes in skin moisture during general anaesthesia for the study and control groups carried out by means of the ANOVA analysis of variance.

Both in the test and control groups, statistically significant differences were found in subsequent skin moisture measurements. Pairwise comparisons indicate statistically significant differences between each pair of measurements. In both groups of patients, there is a clear decrease in skin moisture after induction of anaesthesia compared to the measurement performed before general anaesthesia. The skin moisture values are reduced in subsequent measurements, however the difference is much lower.

Table V presents the results of dependence between skin moisture and the age of the examined patients. Statistical analysis was based on the correlation of r-Pearson.

In the study group there was a statistically significant correlation between skin age and moisture before anaesthesia (stage 1). The older the subject, the lower the skin moisture. However, there were no statistically significant correlations between patients' age and skin moisture in the remaining stages of the study.

In the control group, negative measurements were recorded in all the measurements, the older the patient, the lower the skin moisture.

Table VI shows the skin moisture scores in patients in the test and control groups at individual stages of general

Table V. Correlation of skin moisture with the age of the examined patients

Skin moisture	Correlations with the age of the respondents			
	Study group		Control group	
	r	p	r	p
Before anaesthesia	-0.214	0.043	-0.387	<0.001
After induction for anaesthesia	-0.060	0.573	*-0.322*	*0.002*
15 minutes after skin incision	-0.027	0.802	*-0.368*	*<0.001*
after waking up	-0.093	0.385	*-0.354*	*0.001*

Table VI. Skin moisture in the test and control group during general anaesthesia.

Skin moisture	Study group		Control group		Analysis of differences	
	M	SD	M	SD	t	p
Before anaesthesia	*59.10*	*11.48*	*64.38*	*9.98*	*-3.290*	*0.001*
After induction for anaesthesia	*45.69*	*10.10*	*49.77*	*7.98*	*-3.003*	*0.003*
15 minutes after skin incision	*38.98*	*8.04*	*41.75*	*6.61*	*-2.516*	*0.013*
After waking up	*33.63*	7.38	37.15	5.22	-3.701	<0.001

anaesthesia. The following analysis was carried out using the Student's t test to compare the mean values between the independent groups analysed.

At each stage of the study, a statistically significant difference in skin moisture between the test and control groups was noted. The control group is characterized by a higher skin moisture compared to patients in the study group.

Table VII presents the results of skin moisture measurements in patients qualified to the ASA1 group and the ASA2 and 3 groups. The results were carried out using the Student's t-test for independent tests.

There were statistically significant differences in skin moisture only before general anaesthesia between ASA1 and ASA2 and 3 subjects. No statistically significant differences were noted in the remaining stages of the study.

DISCUSSION

During general anaesthesia, the metabolic rate is reduced by about 20%. General anaesthesia also affects changes in thermoregulation, tenfold increases the range of the permissible target temperature in the hypothalamus. Skin moisture changes are one of the important parameters for the evaluation of thermoregulation. In the conducted skin moisture tests in patients undergoing general anaesthesia, statistically significant differences between the individual stages of the measurements were observed. Decreases in skin moisture during general anaesthesia indicate a reduction in the metabolic rate, as well as the addition of mild hypothermia, which leads to an increase in the level of catecholamines in the circulation, and thus to shrinkage of blood vessels. Perioperative hypothermia is a common phenomenon, which is also noticed by other authors [6, 7].

An important reason for the drop in skin moisture during general anaesthesia is the body's reaction to operational stress. Regardless of the type of agents used for general anaesthesia, they do not have a significant effect on the neuroendocrine or cytokine stress response of the body [8,9,10]. Activation of the sympathetic system leads to the shrinking of skin vessels, hence the skin's moisture content [11]. In the own study, the greatest decrease in skin moisture was observed between measurement I (before induction to anaesthesia) and measurement II (after introduction into anaesthesia). This may indicate a lot of stress for the organism associated with tracheal intubation, where catecholamines are excreted and the peripheral blood vessels shrink. However, some authors have observed increased skin moisture and increased sweating in response to stress associated with intubation [12].

While conducting measurements of skin moisture during general anaesthesia, the lowest values were observed after waking up. One of the mechanisms may have been a decrease in cardiac output following induction to anaesthesia, which resulted in reduced blood flow through the subcutaneous venous plexus, supplying blood with blood capillaries. The consequence of this is the drop in skin moisture observed in own studies. Another very likely factor in the decrease in skin moisture was the use of atropine against polymigmin, which is used to reverse residual muscle relaxation. Atropine is responsible for reducing the secretion of saliva, secretion in the bronchial tree and sweat.

In the control group, as in the studied group, decreases in skin moisture during general anaesthesia were observed. At each stage of the tests, these values were statistically significant.

Table VII. Changes in skin moisture in patients with ASA 1 and ASA 2 and 3.

Skin moisture	ASA 1		ASA 2 – ASA 3		Analysis of differences	
	M	SD	M	SD	t	p
before anaesthesia	63.51	10.10	59.72	11.78	*2.329*	*0.021*
after induction for anaesthesia	48.59	8.62	46.74	9.99	1.332	0.185
15 minutes after skin incision	40.99	7.63	39.65	7.25	1.210	0.228
after waking up	36.24	6.22	34.41	6.95	1.864	0.064

In own studies one can see the dependence of skin moisture on the patient's age, the older the patient the lower is the skin moisture content. Such results in the study group were observed only before introduction into anaesthesia. At the subsequent stages of the measurements there were no statistically significant differences in skin moisture between older and younger patients. Lower skin moisture in elderly patients is the result of, inter alia: reducing the thermoregulatory ability at the level of the hypothalamus, reducing metabolism, reducing the skin's blood supply, as well as being associated with impaired elasticity of blood vessels, as demonstrated by Rida et al. [13].

A relatively common cause of lower skin moisture in elderly patients is insufficient hydration or dehydration. The factors predisposing to insufficient hydration are swallowing disorders resulting from the presence of neurological diseases, apathy, depression, decreased thirst feeling, drug therapy with diuretics, or laxatives taken due to constipation. They observe dryness of mucous membranes, dry skin, hypotonia, tachycardia, oliguria, CNS disorders such as confusion, hallucinations, anxiety, agitation. The effects of long-term dehydration are, among others, necrotic changes in blood vessels in the CNS, thrombosis and focal necrosis of nerve tissue [14, 15].

In the body's aging process physiological changes affect the ability to maintain thermal homeostasis. The regulation of body temperature depends on many organs and systems whose function with age becomes impaired. The main anatomical elements affecting the control are associated with the circulatory, respiratory, nervous systems, structural changes of the skin, or metabolic changes [16,17].

In own studies, the skin moisture measured with Corneometer shows a clear difference in skin moisture in elderly patients compared to younger patients. McLellan et al. [18] similarly in a non-invasive manner studied the effect of skin aging on the function of heat exchange and blood flow, and thus on skin moisture.

In the control group slightly different results were obtained, in all measurements there were statistically significant differences in skin moisture between the elderly and younger patients. Older patients were characterized by a lower value of skin moisture at each stage of the measurement.

In own research the skin moisture measurement using the CM 825 Corneometer for indirect assessment of the hydration status of patients was used. The skin moisture of patients receiving intravenously 500 ml of fluid an hour before anaesthesia was higher compared to the skin moisture of patients prepared for anaesthesia in a standard manner. Additional hydration before general anaesthesia improves the capillary inflow and blood flow. The improvement of cardiovascular efficiency increases the blood supply to the skin, which affects its moisture. At each stage of the study, a statistically significant difference in skin moisture was noted. The above measurements clearly indicate a greater hydration of patients belonging to the control group.

The hydration status of patients during general anaesthesia has a significant impact on the course of surgery and the postoperative period. One of the methods postulated by many authors as non-invasive and practical in use is multi-frequency electrical bio impedance, which is used to assess the hydration status of patients. It allows to assess the size of water spaces, and is based on the use of alternating current in the range of low and high frequencies [19,20].

In the study, patients from the control group received 500 ml of Ringer's or Sterofundin an hour before anaesthesia. The purpose of this procedure was to reduce the early symptoms of inadequate hydration resulting, among others, from the nutrition grace period, the need to prepare the intestines for surgery, as well as to reduce the symptoms of dehydration in the elderly. Such an amount of fluid administered before general anaesthesia, the authors considered optimal for elderly patients with coexisting diseases and organ dysfunction. These patients are usually susceptible to disturbances of acid-base and water-electrolyte balance, resulting both from disorders of tissue perfusion, respiratory failure and metabolic disorders [21].

Another parameter assessed in the presented study was the comparison of skin moisture between patients qualified to the ASA 1 group and patients with ASA 2 and 3. Statistically significant relationships were noted only in study I (before general anaesthesia), where patients from the ASA1 group were characterized by a higher skin moisture compared to ASA 2 and 3. At the remaining stages of the study, this statistical significance was not obtained. The majority of patients qualified for ASA 2 and 3 are elderly patients, burdened with numerous neurological disorders, therefore taking medications that affect the hydration of the body and skin moisture.

The main assumption of the tests carried out to assess the skin moisture of patients undergoing general anaesthesia and to

indirectly assess the thermoregulation was the use of apparatus that allows measurements to be made in a non-invasive, fast and reproducible manner. This method has some drawbacks and limitations, however, the speed and precision of the measurements seemed to be crucial to monitor the above parameters.

CONCLUSIONS

1. Measurement of skin moisture can be used as one of the parameters to assess perioperative stress and changes in body temperature during general anaesthesia, which indirectly determines the functioning of the hypothalamus.
2. By measuring the skin's moisture it is possible to indirectly assess the hydration status of patients and decrease the metabolism during general anaesthesia.
3. The decrease in skin moisture during general anaesthesia is the effect of changes in central and peripheral thermoregulation.

REFERENCES

1. Uhrig L, Dehaene S, Jarraya B. Cerebral mechanism of general anesthesia. Annales Francaises d' Anesthesie et de Reanimation. 2014;2(33):72-82.
2. Drobnik L. Pooperacyjne powikłania neurologiczne. In: Karpel E, Jałowiecki P (eds). Ogólne powikłania pooperacyjne. Warszawa: PZWL, 2009, 229-249.
3. Torossian A. Thermal management Turing anaesthesia and thermoregulation standards for the prevention of inadvertent perioperative hypothermia. Best Prac Res Clin Anest. 2008;22(4):659-668.
4. Konturek SJ. Regulacja temperatury ciała przez równowagę między ilością ciepła wytworzonego i ilością ciepła oddanego. In: Fizjologia człowieka. Wrocław: Elservier Urban § Partner. 2013, 495-499.
5. Contractor S, Hardman JG. Injury During anaesthesia. CEACCP 2006; 6:67-68.
6. Forbes S, Eskicioglu C, Nathens A. Evidence-besed guidelines for prevention of perioperative hypothermia. J Amer Col Surgen. 2009;209:492-503.
7. Zygoń J, Gołąbek-Dropiewska K, Sowa M et al. Technika Fast-Track – zastosowanie u pacjentów poddawanych elektywnym operacjom jelita grubego. J Oncol. 2011;61:150-158.
8. Braz MG, Braz IG, Braz JR et al. Comparison of oxidative stress in ASA physical status I patients Schedule for minimally invasive surgery under balanced or intravenosus anesthesia. Minerva Anestesiologica 2013;79(9):1030-1038.
9. Kahveci K, Ornek D, Doger C et al. The effect of anesthesia type on stress hormone response: Comparison of general versus epidural anesthesia. Niger J Clin Pract. 2014;17(4):523-527.
10. Milosavljevic SB, Pavlovic AP, Trpkovic SV, Ilić AN, Sekulic AD. Influence of spinal and general anesthesia on the metabolic, hormonal and hemodynamic response in elective surgical patients. Med Scien Monit. 2014;20:1833-1840.
11. Morrison SF.: Central thermoregulation. Primer on the Autonomic Nervous System 2012;8:243-247.
12. Riad W, Schreiber M, Saeed AB. Monitoring with EEG entropy decreases propofol requirement and maintains cardiovascular stability during induction of anaesthesia in elderly patients. European Journal of Anaesthesiology 2007;24:684-688.
13. Rida M, Ghaddar N, Ghali K, Hoballah J. Elderly bioheat madeling: Changes in physiology Thermoregulation and blood flow circulation. Internat J Biometeorol. 2014;7:1-19.
14. Shah MK, Workeneh B, Taffet GE. Hypernatremia in the geriatric population. J Clin Interv Aging. 2014; 19(9): 1987-1992.
15. Fiaux E, Noel D, Armengol G et al. Usefulness of assessing hydration status in elderly patients over 70 years with suspected deep vein thrombosis. Rev Méd Inter. 2014;10(7):267-273.
16. Blatteirs CM. Age – dependent changes in temperature regulation – A mini revive. Gerontology 2012;58(4):289-295.
17. Van Someren EJW. Age – related changes in thermoreception and thermoregulation. Handbook Biol Aging 2011;3:463-478.
18. McLellan K, Petrofsky JS, Baings G, Zimmerman G, Prowse M, Le S. The effects of skin moisture and subcutaneous fat thickness on the ability of the skin to dissipate heat in young and old subjects with and without diabetes , at three environmental room temperatures. Med Engineer Physics J. 2009;31(2): 165-172.
19. Załuska W. Sucha masa ciała – stary problem, nowe metody. For Nefrol. 2011;4(2):100-103.
20. Van Biesen W, Williams JD, Covic AC et al. EuroBCM Study Group. Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBMC) study cohort. PloS One 2011;6(2):17148.
21. Gaszyński T, Małachowska B, Wieczorek A. Badanie płynów stosowanych w płynoterapia okołooperacyjnej – analiza obecnie stosowanej praktyki. Anest Rat. 2012;(6):262-267.

Conflict of interest:
All authors declare no coflict of interest

CORRESPONDING AUTHOR

Gustaw Wójcik
Department of Physiotherapy
Institute of Physical Education and Physiotherapy
Pope John Paul II State School of Higer Education in Biała Podlaska
e-mail: gustww@tlen.pl

Received: 13.03.2019
Accepted: 08.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

ROLE OF IMMUNE SYSTEM IN DEVELOPMENT AND PROGRESS OF COMBINED ARTERIAL HYPERTENSION AND GOUT

Oleg A. Bychkov[1], Vitalii E. Kondratiuk[1], Nina G. Bychkova[1], Zemfira V. Morozova[1], Svetlana A. Bychkova[2], Alina P. Tarasiuk[1]

[1] BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2] UKRAINIAN MILITARY MEDICAL ACADEMY, KYIV, UKRAINE

ABSTRACT

Introduction: Multiple data available indicate high prevalence of comorbid abnormalities in gouty arthritis patients, namely, high incidence of arterial hypertension, coronary artery disease, stroke, atherosclerosis of carotid arteries, vascular dementia. For instance, hypertension is found in 36-41% gout patients, and combined with metabolic syndrome it may reach 80%.

The aim: Studying features of clinical course, lipid profile and immune status in patients with combined hypertension and gout.

Materials and methods: The study involved examination of 137 male patients with stage II hypertension, average age 56.9±3.4. All patients underwent echocardiography with estimation of the left ventricular mass index to verify hypertension stage, blood chemistry test with estimation of uric acid level, as well as lipid profile and immune status.

Results: We have found significant disorders in the lipid profile of blood serum in patients with combined hypertension and gout. Positively higher percentage of activated T-cells was found in patients with combined hypertension and gout, both with early (CD3+CD25+) and late (CD3+HLA-DR+) activation marker, as well as those expressing FAS receptor, and ready to enter into apoptosis.

Conclusion: We have identified abnormalities in adhesion and cooperation of immune competent cells, resulting in more intense activation of the same, effector functions and migration to the area of inflammation in the vessel wall.

KEY WORDS: arterial hypertension, gout, cytokines, cellular immunity

Wiad Lek 2019, 72, 7, 1295-1299

INTRODUCTION

Gout is one of the most common rheumatic diseases found in adults. Contemporary epidemiological studies indicate that its prevalence is growing not only in the countries with high living standards but also in the regions where it has formerly been deemed a fairly rare disease [1, 2]. The latest trend is the more aggressive clinical course of gout, manifesting itself in a larger number of affected joints, nephrolithiasis and frequent development into chronic arthritis. At the same time occurrence of gout in females and in families, as well as nephrolithiasis has grown [3]. Multiple data available indicate high prevalence of comorbid abnormalities in gouty arthritis patients, namely, high incidence of arterial hypertension, coronary artery disease (CAD), stroke, atherosclerosis of carotid arteries, vascular dementia [4, 5]. For instance, hypertension is found in 36-41% gout patients, and combined with metabolic syndrome (MS) it may reach 80% [6, 7]. In the USA 74% gout patients (6.1 million people) suffer from hypertension, and in the East-European countries hypertension is found in the ¾ of gout patients, total frequency of MS being 57% (from 15 to 77%) [8].

Gout is viewed as a systemic tophus-type disease characterized by deposition of monosodium urate crystals in various tissues and inflammation developing in patients affected by hyperuricemia, which is associated with ambient and/or genetic factors [1, 3]. Gout progress is caused by uncontrolled hyperuricemia, which seems the only independent gout risk factor, with the risk growing simultaneously with hyperuricemia progress [4]. However, diagnostic relevance of hyperuricemia in identification of gout is not in any way equal to the same of monosodium urate crystals: frequency of identification of hyperuricemia in population exceeds frequency of gout by a large margin.

The problem of hypertension combined with metabolic disorders is highly significant [9, 10]. Connection between uric acid level and cardiovascular diseases has been studied in at least 20 epidemiological and clinical trials involving over 100,000 patients with hypertension. In more than a half of the studies (11 out of 20) an independent connection was found between uricemia and risk of cardiovascular diseases, at least in main subgroups. Findings suggest that uric acid level contributes greatly to cardiovascular risk in patients with unattended

hypertension. It was demonstrated that hyperuricemia increases the risk of hypertension development and progress. It was shown that rise in uric acid level by 1 mg/dl was accompanied by rise in hypertension risk by 13%, the risk greatly increasing in younger people and in females [4, 6, 7].

It was found that rise in uric acid level in patients with hypertension was an independent predictor for rise in risk of cardiovascular events (including fatal) and total mortality [11]. It was proved that the main cause of mortality in gout patients was specifically cardiovascular diseases, and it was shown that gout was connected with high risk of total and cardiovascular mortality [11, 12] and with increased risk of development of myocardial infarction in gout patients [8].

In view of growing incidence of gout in young and middle-aged patients, the problem of diagnostics and treatment of cardiovascular diseases in this category of patients is a subject of intense study. A number of studies indicate a tight link between insulin resistance and hyperuricemia and describe mechanisms by which hyperinsulinemia and insulin resistance may increase concentration of urates in blood serum [9, 10].

THE AIM

Thesis objective – studying features of clinical course, lipid profile and immune status in patients with combined hypertension and gout.

MATERIALS AND METHODS

The study involved examination of 137 male patients with stage II hypertension, average age 56.9±3.4. The main group consisted of 72 patients with combined hypertension and gout, and comparison group consisted of 65 patients with hypertension. The study also included examination of 35 healthy people of similar age and sex without any symptoms of hypertension or gout. Hypertension was diagnosed based on recommendations of the Ukrainian Association of Cardiologists and on Guideline and Clinical Protocol for Arterial Hypertension [13], gout was diagnosed based on recommendations of the Decree No. 676, and metabolic syndrome was identified based on IDF criteria, 2005 [10]. Written informed consent was obtained from all patients before they had started in the study in accordance with the provisions of the Helsinki Declaration; the study protocol had been agreed with the Byoethics Commission of Bogomolets National Medical University. All patients underwent echocardiography with estimation of the left ventricular mass index (LV mass index) to verify hypertension stage, blood chemistry test with estimation of uric acid level, as well as lipid profile with estimation of total cholesterol and its fractions – high-density lipoproteins (HDL-C), low-density lipoproteins (LDL-C), very low-density lipoproteins (VLDL-C) and triglycerides (TG). Levels of pro-inflammatory and anti-inflammatory cytokines, Interleukin-17A (IL-17A), Interferon gamma (IFN-γ), content of soluble cell adhesion molecules sICAM-1 and sVCAM were determined using immunoassay kits certified in Ukraine and applying methods suggested by manufacturers Pro Con (Russia) and Diaclon (France), level of transforming growth factor beta (TGF-β) - using methods by Genzyme diagnostics. Content of lymphocyte subpopulations with CD3+CD25+, CD3+CD95+, CD3+HLA-DR+, CD54+, CD11b+ and CD62L+ phenotypes was determined by indirect immunofluorescence using monoclonal antibodies [14]. Student's t-test (variation statistics) was applied to statistical data analysis using Microsoft XP Excel applied software and specialized software STATGRAPHICS Plus v. 2.1.

RESULTS AND DISCUSSION

Main results of the comprehensive examination of patients with combined abnormalities are given in Table I. These data suggest that there were no reliable differences ($p>0.1$) in duration of the disease in patients of both groups, as well as in levels of office systolic and diastolic blood pressure, heart rate and LV mass index ($p>0.1$). Patients in the main group demonstrated positively higher levels of body mass index (BMI) with prevailing stage II obesity and waist circumference over 94 cm, which in combination with hypertension and lipid profile disorders became a reason for diagnosing them with MS. Thus, MS symptoms were found in 87.5% patients in the main group (63 pers.) and 63.08 % (41 pers.) patients in the comparison group. The main group also demonstrated positively higher rate of occurrence of concurrent chronic heart failure (CHF) (functional NYHA class I-II).

Based on analysis of the data given in Table I, we can conclude that uric acid level in the main group of patients was positively higher by 61.12% ($p<0.05$) than in the comparison group. Study of the lipid profile in the main group of patients showed significantly higher TG content – by 29.90% ($p<0.05$), VLDL-C – by 19.51% ($p<0.05$) than in the comparison group, as well as positively higher value of atherogenic index – by 17.01% ($p<0.05$). There were no significant differences in cholesterol and HDL-C. These data stemmed from common pathogenic mechanisms of atherosclerosis and hypertension development, role of atherosclerotic processes in blood pressure rise mechanisms. Certainly, such patients should be provided with follow-up care and not only diet, but also specific lipid-lowering therapy.

Based on examination findings it was established that patients in the main group and in the comparison group had significant disorders of the immune status and cytokine profile of the blood serum (Table II).

Based on analysis of the data given in Table II, we can conclude that level of activated T-cells with CD3+CD25+ phenotype in the main group of patients was positively higher by 32.57% ($p<0.05$) than in the comparison group, which indicates that development of inflammation in the joints simultaneously with atherosclerotic inflammation and endothelium dysfunction generates a stronger immune response with obvious T-cell activation. Main group

Table I. Clinical, Instrumental and Laboratory Findings in Patients with Combined Hypertension and Gout (M±m)

Values	Main group (n=72)	Comparison group (n=65)	Control group (n=35)
Duration of hypertension, years	10.2 ± 1.2	10.5 ± 1.3	(-)
Systolic BP, mm Hg	167.7 ± 2.1*	163.5 ± 2.7*	125.6±4.7
Diastolic BP, mm Hg	102.7 ± 2.3*	98.1 ± 2.1*	75.2±3.7
Pulse, bpm	72.6±2.7	74.3±2.8	73.7±3.9
LV mass index, g/m^2	132.6±3.6*	130.4±3.7*	81.1±2.3
BMI, kg/m^2	32.7±1.9*	27.2±1.7* **	22.3±2.8
Concurrent CHF (NYHA FC I-II)	37 (51.4%)	22 (33.9%)	(-)
Uric acid	479.5±30.8*	297.6±25.9 **	265.5±12.3
Total cholesterol, mmol/l	7.03±0.31*	6.95±0.23*	4.90±0.41
TG, ммоль/л	2.78±0.14*	2.14±0.11* **	1.18±0.12
LDL-C, mmol/l	3.72±0.19*	3.66±0.22*	2.81±0.35
HDL-C, mmol/l	1.01±0.03*	1.04±0.02*	1.49±0.21
VLDL-C, mmol/l	0.98±0.06*	0.82±0.07* **	0.51±0.07
Atherogenic index	5.78±0.11*	4.94±0.16* **	3.14±0.24

Notes: * - significance of differences in values compared with control group ($p<0.05$); **- significance of differences in values between groups; n – number of patients.

Table II. Immune and Cytokine Status in Patients with Combined Hypertension and Gout (M±m)

Values	Main group (n=72)	Comparison group (n=65)	Control group (n=35)
CD3+CD25+ lymphocytes, %	23.2±1.13	17.50±0.77**	14.71±0.39
CD3+HLA-DR+ lymphocytes, %	24.8±1.09	18.6±0.72**	15.4±0.72
CD3+CD95+ lymphocytes, %	15.7±0.63	11.8±0.44**	6.12±0.11
CD54$^+$ lymphocytes,%	19.2±0.73	15.1±0.48**	11.07±1.65
CD11b$^+$ lymphocytes,%	37.2±1.81	26.9±1.69**	21.5±1.4
CD62L$^+$ lymphocytes,%	40.5±1.73	35.6±1.69**	28.3±1.7
CD30+ lymphocytes, %	2.73±0.015	2.69±0.018	1.8±0.03
TNF-α, pg/ml	129.6±4.38	102.7±5.23**	42.3±4.9
IL-1β, pg/ml	111.8±5.24	96.6±5.35**	39.42±4.5
IL-6, pg/ml	70.4±2.41	69.9±2.93	10.31±2.3
IL-8, pg/ml	23.5±1.07	22.1±1.15	12.7±1.5
IFN-γ, pg/ml	48.6±2.96	47.9±2.13	96.4±8.6
IL-4, pg/ml	10.1±0.96	17.3±0.83**	25.42±3.3
IL-10, pg/ml	33.4±2.1	31.7±1.46	41.75±2.8
TGF-β, pg/ml	73.8±3.12	70.3±4.04	39.4±4.1
IL-17A, pg/ml	38.1±2.6	35.3±1.1	17.3±2.7
sVCAM, pg/ml	56.1±2.9	39.3±1.6**	18.6±1.9
sICAM-1, ng/ml	389.4±11.3	328.3±10.4**	275.5±17.29

Notes: **- significance of differences in values between groups; n – number of patients.

of patients also demonstrated positively higher content of activated lymphocyte subpopulations with CD3+HLA-DR+ phenotype exceeding reference range by 33.3% ($p<0.05$), which is a marker of late lymphocyte activation and confirms long duration of inflammation and intensity of immune response. High content of CD3+CD95+ lymphocytes (by 33.05%, ($p<0.05$)) as compared with the group of patients with isolated arterial hypertension is a consequence of pro-apoptotic effect of TNF-α.

The main group of patients also demonstrated positively higher content of activated lymphocyte subpopulations carrying various cell adhesion molecules and receptors thereof. For instance, content of CD54+ lymphocytes expressing cell adhesion molecule ICAM-1 exceeded the

comparison group value by 27.15% ($p<0.05$), CD11b - by 38.29% ($p<0.05$), CD62L - by 13.76% ($p<0.05$). It is CD11b receptor that provides for adhesion of macrophages and neutrophils to the endothelial wall and acts as a ligand for ICAM-1, CD62L (L-selectin) provides for adhesion and adherence of lymphocytes to the endothelial wall [15].

We have also found high serum concentration of soluble vascular cell adhesion molecule sVCAM, the level of which in the main group exceeded the similar value in the comparison group by 42.75% ($p<0.05$), sICAM-1 - by 18.61% ($p<0.05$). Hence, more intense inflammation with high levels of pro-inflammatory cytokines leads to stronger activation of immune competent cells and synthesis of cell adhesion molecules by immune competent cells. Moreover, high serum concentration of soluble vascular cell adhesion molecules sICAM-1 and sVCAM was combined with increased level of ICAM-1 (CD54+) receptor expression on peripheral blood lymphocytes, as well as CD11b (CD54 receptor ligand) and CD62L receptors, which provide for cell attachment to the endothelial wall.

Cell adhesion molecules play a key part in immune response processes and clearly regulate mechanisms of atherosclerotic inflammation development, since they are expressed on some cells of the immune system, bind to their counter receptors and attach to one another, which leads to local accumulation thereof, development of stasis and thrombosis in blood vessels. ICAM-1, VCAM and E-selectin are defined as early markers indicating inflammation activity, especially at the early stages of the disease. ICAM-1 belongs to immunoglobulin family, and its expression is increased by such cytokines as IL-2 and TNF-α. VCAM – vascular cell adhesion molecule – belongs to immunoglobulin family and is expressed on the surface of activated endothelium [15].

Patients with combined abnormalities, as well as patients with isolated hypertension demonstrated positively higher content of CD30+lymphocytes by 51.7% ($p<0.05$) and by 49.4% ($p<0.05$) respectively, which indicates type 2 T-helper immune response prevailing in atherosclerosis-associated diseases and development of autoimmune disorders associated with endothelium dysfunction and development of atherosclerotic inflammation.

It should be noted that the comparison group of patients with stage II isolated hypertension also demonstrated significant changes in the content of activated lymphocyte subpopulations as compared with values in healthy individuals. For instance, relative value of CD3+CD25+ lymphocytes was positively higher than the control group value by 18.97% ($p<0.05$), CD3+HLA-DR+ lymphocytes - by 20.78% ($p<0.05$), CD3+CD95+ lymphocytes - by 92.81% ($p<0.05$). The comparison group of patients also demonstrated significant increase in the value of lymphocytes expressing various cell adhesion molecules: level of CD54+ lymphocytes exceeded the control group value by 36.40% ($p<0.05$), CD11b - by 25.12% ($p<0.05$), CD62L - by 25.83% ($p<0.05$).

It is commonly known that hypertension causes thickening of the middle layer, narrowing of the lumen and increase in extracellular matrix [11]. Rise in the mass of smooth muscle cells increases the degree of vasoconstriction influenced by neurohormones and leads to rise in the total peripheral resistance, which in its turn contributes to stabilization and exacerbation of hypertension. Vessel wall thickening and its leukocytic infiltration by activated cells and cell adhesion molecules is a precondition for development and progress of atherosclerosis [11, 15].

TNF-α value in patients with combined hypertension and gout was 3.6 times higher ($p<0.05$) than the value in healthy individuals and exceeded the value in the comparison group by 26.19% ($p<0.05$); IL-1β – 2.84 times higher and by 15.73% ($p<0.05$) respectively. IL-6 value was 6.83 times higher than the reference range and had no significant differences from the comparison group value ($p>0.1$). Similar changes were found in IL-8 value, which was 1.85 times higher than the control group value ($p<0.05$), IL-17A - 2.2 times higher ($p<0.05$), and IFN-γ value was lower than the value in healthy individuals by 50.41% ($p<0.05$). At the same time we have also found significant rise in serum concentration of TGF-β in the main group – 1.87 times higher ($p<0.05$) than the control group value, and 1.78 times higher ($p<0.05$) than the comparison group value. These data may be due to the fact that TNF-α is viewed as a mediator of insulin resistance associated with obesity, which reduces activity of insulin receptor tyrosine kinase and inhibits activity of intracellular glucose transporters in muscle and adipose tissues. Symptoms of metabolic syndrome and possible development of non-alcoholic fatty liver disease in patients with hypertension also contribute to specific changes in the immune system, since a large scope of data concerning involvement of immune mechanisms in pathogenesis of atherosclerosis accumulated over the last years and immune theories of atherogenesis were suggested [15]. Lasting antigen persistence, namely low-density lipoproteins, both free and as a part of circulating immune complexes (CIC), is highly relevant for evolution of atherosclerosis, cytokine interactions between CD3+ lymphocytes and monocytes/macrophages. Phagocyte activation promotes release of hydrolytic enzymes, cytokines, chemokines and growth factors. Inflammation changes drastically further metabolism of low-density lipoproteins in the blood vessel wall – TNF-α and IL-1 enhance binding of low-density lipoproteins (LDL-C) with endothelium and smooth muscle cells [11, 15]. TGF-β is produced by macrophages, lymphocytes and dendritic cells, and in liver – by liver-recruited macrophages and Kupffer cells, and plays a key part in immune homeostasis regulation, its main effects are connected with inhibition of T-cell and B-cell proliferation, namely cytotoxic CD8+ lymphocytes, type 1, 2 and 17 T-helpers, IL-2 and IL-12 secreted by T-cells. Defects in TGF-β signalling pathways contribute to increased proliferation and effector function of immune cells and may cause an uncontrolled immune response. In pathological conditions TGF-β is a fibrosis inducer and enhances collagen synthesis by hepatic stellate cells. The studies proved that TGF-β identified differentiation of stellate cells into microfibroblasts and directly influenced synthesis of collagens, tissue inhibitors

of metalloproteinase 1, plasminogen activator inhibitor 1 and other factors [4], and hence its level in blood serum is highly relevant for identification of hepatic fibrosis at the early stages and development of the disease into hepatic cirrhosis and hepatocellular carcinoma.

Level of anti-inflammatory cytokines IL-4 and IL-10 in both groups was positively lower than the control group value. However, in patients with combined hypertension and gout IL-4 level was significantly lower in the main group by 71.29% ($p<0.05$) than in the comparison group, which is a compensatory response to higher serum concentrations of pro-inflammatory cytokines.

CONCLUSIONS

In summary, we have found significant disorders in the lipid profile of blood serum in patients with combined hypertension and gout and positively higher level of triglycerides and very low-density lipoproteins, as well as atherogenic index. Moreover, waist circumference in most of the patients in this group exceeded 94 cm, which in combination with hypertension and lipid profile disorders became a reason for diagnosing 87.5% patients in the main group (63 pers.) and 63.08 % (41 pers.) patients in the comparison group with MS.

Positively higher percentage of activated T-cells was found in patients with combined hypertension and gout, both with early (CD3+CD25+) and late (CD3+HLA-DR+) activation marker, as well as those expressing FAS receptor, and ready to enter into apoptosis. We have identified abnormalities in adhesion and cooperation of immune competent cells, resulting in more intense activation of the same, effector functions and migration to the area of inflammation in the vessel wall. Expression of cell adhesion molecules on endothelium and lymphocytes is a primary stage of their recruitment to the area of inflammation, is accompanied by a wide range of immunological responses, defensive in their nature, but which cause necrotic or dystrophic abnormalities due to increased duration or intensity. Moreover, high level of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8) was found in blood serum of patients with combined hypertension and metabolic syndrome, combined with increased type 2 T-helper immune response (low serum concentration of IFN-γ), and type 17 T-helper immune response (high serum concentration of IL-17A). This type of abnormalities in the immune system is typical in patients with combined hypertension and gout.

REFERENCES

1. Hui M., Carr A., Cameron S. et al. The British Society for Rheumatology Guideline for the Management of Gout. Rheumatology, Vol. 56, Is. 7, 1 July 2017; p. e1-e20. Doi:10.1093/rheumatology/kex156
2. Kuo C.F., Grainge M.J., Mallen C. et.al. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann Rheum Dis. 2016;75(1):210–7. doi: 10.1136/annrheumdis-2014-206410.
3. Kuo C.F., See L.C., Yu K.H. et al. Significance of serum uric acid levels on the risk of all-cause and cardiovascular mortality. Rheumatology (Oxford) 2013;52(1):127–134. doi: 10.1093/rheumatology/kes223.40.
4. Mancia G., Grassi G., Borghi C. Hyperuricemia, Urate Deposition and Association with Hypertension. Curr. Med. Res. Opin. 2015; 2(31):15-19.
5. Kondratiuk, V.E., Synytsia, Y.P., Karmazina, O.M. Structural and functional impairments of the left cardiac cavities in patients with gout and essential hypertension. General Medicine. 2018; 3(20):3-7.
6. McAdams-DeMarco M.A., Maynard J.W., Baer A.N. Coresh J. Hypertension and the risk of incident gout in a population-based study: the atherosclerosis risk in communities cohort. J Clin Hypertens (Greenwich) 2012;14(10):675–9. doi: 10.1111/j.1751-7176.2012.00674.x.
7. Markelova E.I., Yeliseyev M.S., Barskova V.G. Arterial Hypertension in Gout Patients: Principles of Pathogenisis, Clinical Significance, Diagnostics. Contemporary Rheumatology. 2012; 43: 23-30.
8. Perez-Ruiz F., Becker M.A. Inflammation: Possible Mechanism for Causative Role of Hyperuricemia/Gout in Cardiovascular Disease. Curr. Med. Res. Opin. 2015; 2(31), Suppl. 2. – P. 9-14.
9. Rho Y.H., Lu N., Peloquin C.E. et al. Independent impact of gout on the risk of diabetes mellitus among women and men: a population-based, BMI-matched cohort study. Ann Rheum Dis. 2016;75(1):91–5. doi: 10.1136/annrheumdis-2014-205827.
10. Siniachenko O.V. Metabolic Syndrome Associated with Gout. Internal Medicine. 2007; 3:119-124.
11. Bagriy A.E. Arterial Hypertension and Cardiovascular Risk. In: Diadyk O.I., Zharinov O.I., Bagriy A.E. et al. Kyiv: The 4th Wave; 2009, p. 160.
12. Kondratiuk V.E., Synytsia Y.P. Effect of quercetin on the echocardiographic parameters of left ventricular diastolic function in patients with gout and essential hypertension. Wiad Lek. 2018; 71(8):1554-1559.
13. Netiazhenko V.Z. Guideline and Clinical Protocol for Arterial Hypertension-Related Medical Services. Kyiv; 2012, p.107.
14. Perederij V.G. Immune Status, Principles of its Detection and Correction of Immune Disorders. In: Perederij V.G., Zemskov A.M., Bychkova N.G. et al. Kyiv: Zdorovja; 1995, p.211.
15. Zalesskiy V.N. Autoimmune and Immune Inflammatory Processes Associated with Atherosclerosis, Its Nutrition-Based Prevention and Treatment: Monograph. In: Zalesskiy V.N., Gavrilenko T.I. Kyiv: Vipol; 2008, p.592.

The work was performed as part of the research study of the Department of Propaedeutic of internal medicine №2 "Gout, hyperuricemia and associated comorbidity: clinic, diagnosis, new approaches to treatment" (State registration number 0116U000125).

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Oleg Bychkov
Department of Propaedeutic of internal medicine №2,
Bogomolets National Medical University
T. Shevchenko boulevard, 13, 01601 Kyiv, Ukraine
tel: +380962941359
e-mail: oleg_bichkov@yahoo.com

Received: 21.02.2019
Accepted: 07.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

THE INFLUENCE OF DRUG TREATMENT ON CARDIO-VASCULAR SYSTEM OF THE RATS WITH CONGENITAL HYPOTHYROIDISM

Svetlana Chuhray[1], Viktoria Lavrynenko[2], Rostyslav Kaminsky[1], Olena Ustymenko[1], Iryna Dzevulska[1], Ruzhena Matkivska[1], Oleksandr Kovalchuk[2], Olena Holubchenko[1], Liudmyla Sokurenko[1, 2]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2]TARAS SHEVCHENKO NATIONAL UNIVERSITY OF KYIV, UKRAINE

ABSTRACT

Introduction: In the treatment of hypothyroidism substitution therapy with L-thyroxine is used, it is also advisable to use the metabolites with membrane-stabilizing properties that normalize the metabolism in the body, for example, calcitonin, which significantly reduces the depth of the dystrophic phenomena in the myocardium.

The aim was to study the patterns of structural changes in the left ventricular myocardial capillaries of rats with congenital hypothyroidism in combinative drug therapy with L-thyroxine and calcitonin.

Materials and methods: 30 white Wistar line rats were used as experimental animals: 10 with treatment and 10 without as well as control – 10 intact Wistar line rats of the same age. Mercazolil was used to inhibit thyroid gland in order to model congenital hypothyroidism. After birth, the rats received L-thyroxine at a dose of 10 μg / kg per os daily, calcitonin at a dose of 1.0 MU / kg per day intramuscularly, then with mother's milk, later by themselves for 100 days. The arterial pressure was measured in all experimental groups during extraction from the experiment by plethysmograph, their left ventricular myocardium was examined under electron microscope and micropinocytotic vesicles in their cells were studied morphometrically.

Results: In rats with congenital hypothyroidism, for which L-thyroxin drug in combination with calcitonin was used as a substitution therapy, after pharmacological correction, in general there is no pronounced heteromorphism of the ultrastructure of the left ventricular myocardial blood capillaries, which was characteristic for animals without pharmacological correction. The analysis showed normalization of the content of free thyroxine in blood plasma and blood pressure of rats with congenital hypothyroidism after complex substitution therapy.

Conclusions: In rats with congenital hypothyroidism, which received L-thyroxine and calcitonin at birth, the myocardium capillaries generally remain intact and have morphological and functional characteristics similar to intact animals, which is the theoretical basis for the need for calcitonin to be used in substitution therapy in hypothyroidism.

KEY WORDS: myocardium, blood capillaries, rat, hypertension, electron microscopy, L-thyroxine, calcitonin

Wiad Lek 2019, 72, 7, 1300-1303

INTRODUCTION

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth and exact cause for the vast majority of cases of thyroid dysgenesis remains unknown, but management of CH is based on restoring thyroid function to normal, not necessarily knowing the exact underlying cause [1].

In the treatment of hypothyroidism substitution L-thyroxine therapy is used, which, according to some authors, has a positive effect on the level of arterial pressure [2, 3]. It is also advisable to use the metabolites with antioxidant membrane-stabilizing properties, that normalize the metabolism in the body [4, 5]. Experimental studies have shown that monotherapy with L-thyroxin only delays the formation of structural and functional changes in the myocardium of rats with thyroid-ectomy but does not prevent them, while the combined treatment significantly reduces the depth of myocardial dystrophic changes [6].

THE AIM

The aim of the study was examination of the patterns of structural changes in the left ventricular myocardial capillaries of the congenital hypothyroidism rats in a combined pharmacotherapy with L-thyroxine and calcitonin.

MATERIALS AND METHODS

30 white Wistar line rats were used for the experiments. All animals were kept in the Bogomolets National Medical University vivarium in standard conditions. Experimental group included 10 sexually-mature (100-day) Wistar CHT rats with treatment and 10 without. Control group included 10 intact Wistar line rats of the same age. The rats were treated with Mercazolil – thyreostatic that inhibited thyroid gland activity thus modeling the congenital hypothyroidism. Pregnant female rats were administered with Mercazolil from the 14th day of perinatal development. After birth, Mercazolil was received with the mother's milk,

Table I. Changes in the content of free thyroxine in blood plasma and AP figures in rats with substitution correction

	Control	CHT	CHT with correction
Arterial pressure, mm Hg	109,4±5,3	131,6±5,2*,**	115,4±5,7
Thyroxine, pmol/l	8,58±0,72	2,77±0,76*,**	8,96±1,39 **

Note: * – p<0, 05 in comparison with the data of the Control;
** – p<0, 05 in comparison with the data of the group without substitution correction.

and later – by self-feeding. Throughout the experiment the daily dose of the drug was 20 mg / kg of body weight. Water was used as a solvent. When control and CHT rats were removed from the experiment, the immune-enzymatic method on the Sunrise RC device, TEKAN was used to control the development of hypothyroidism.

Correction of thyroid hormones deficiency began after birth of rats. Animals received L-thyroxine (Pharmac, Ukraine) at a dose of 10 μg / kg per os daily, calcitonin (a preparation "Miacalcic", a manufacturer of "Novartis", Switzerland) at a dose of 1.0 MU / kg intramuscularly every other day with mother's milk, and then independently for 100 days.

Animal studies were performed according to "General ethical principles of animal experiments", adopted by the First National Congress on Bioethics (Kiev, 2001) as well as the Law of Ukraine "On protection of animals from cruelty" (2006).

When experimental rats were extracted from the experiment, the immune-enzymatic method on the Sunrise RC device, TEKAN was used to control the development of hypothyroidism while AP (arterial pressure) was controlled by plethysmograph.

Left ventricular myocardium of experimental rats was studied under electron microscope. General techniques of electron microscopic examination were used in material processing [7]. Ultratome Reihart (Austria) was used for production of ultra-thin sections that were further studied under electron microscope PEM-125K.

Analysis of all morphometric characteristics was conducted by the program "Organelle" on a semi-automatic graphic research processing device. The characteristics included: volumetric and quantitative densities, cross-section area and form factor of micropinocytotic vesicles (MPV). Student parametric and Kolmogorov-Smirnov nonparametric criteria were used for statistical processing according to the variation statistics principles.

RESULTS

CHANGES IN FUNCTIONAL PARAMETERS IN EXPERIMENTAL RATS

The immune-enzyme analysis showed no significant difference in the content of free thyroxine in the blood plasma of intact rats (8.58 ± 0.72 pmol / l) and rats with congenital hypothyroidism with complex substitution correction (8.96 ± 1.39 pmol / l), as well as blood pressure index (115.4 ± 5.7 mm Hg) (Table I).

ULTRASTRUCTURE OF BLOOD CAPILLARIES OF MYOCARDIUM IN RATS WITH SUBSTITUTIVE CORRECTION

In rats with congenital hypothyroidism, for which the preparation of L-thyroxine in combination with calcitonin was used, the lumen of most left ventricular myocardial circulatory capillaries is enlarged, incompletely filled with finely dispersed substance. The lumen surface of the endothelium is smooth, contains a moderate amount of shallow invaginations and micro-outgrowths (Fig.1, Fig. 2). Peripheral areas of the cells had insignificant thickness.

The nuclei of these endothelial cells are oval, slightly elongated, with a smoothed surface due to the fact that the nuclear membrane does not form deep invaginations. Karyoplasm is sometimes spotty due to the uneven distribution of chromatin, among which, nevertheless, euchromatin predominates.

The cytoplasm contains a large number of mitochondria, ribosomes, tubules of the granular endoplasmic reticulum (Fig. 1, Fig. 2). Mitochondria are represented by structures of mostly round shape and large size. They have a matrix of moderate electron density, which contains intra-mitochondrial membranes – well-structured crystaes, the amount of which varies in different organelles (Fig.1, Fig. 2).

The endoplasmic reticulum is represented by its rough form, its small, moderately enlarged tubules, as well as ribosomes and polysomes, are located throughout the cytoplasm (Fig.1, Fig.2).

As for the characteristic endothelial structures – the bodies of Weibel-Palade, the cytoplasm contains their typical forms, in contrast to rats with congenital hypothyroidism without correction. Interestingly, from our point of view, is that these bodies are present in the endothelium of rats with arterial hypertension after pharmacological correction.

MICROPINOCYTOTIC VESICLES IN ENDOTHELIAL CELLS OF MYOCARDIAL BLOOD CAPILLARIES IN RATS WITH SUBSTITUTIVE CORRECTION

In nuclei of cells with signs of active transport chromatin is distributed unevenly, mainly under the membrane. Micropinocytotic vesicles are found both attached to the basal or lumen membranes or detached (Fig.1, Fig. 2). Their quantitative density is statistically the same with control parameters and significantly differs from the indicators in untreated animals (Table II).

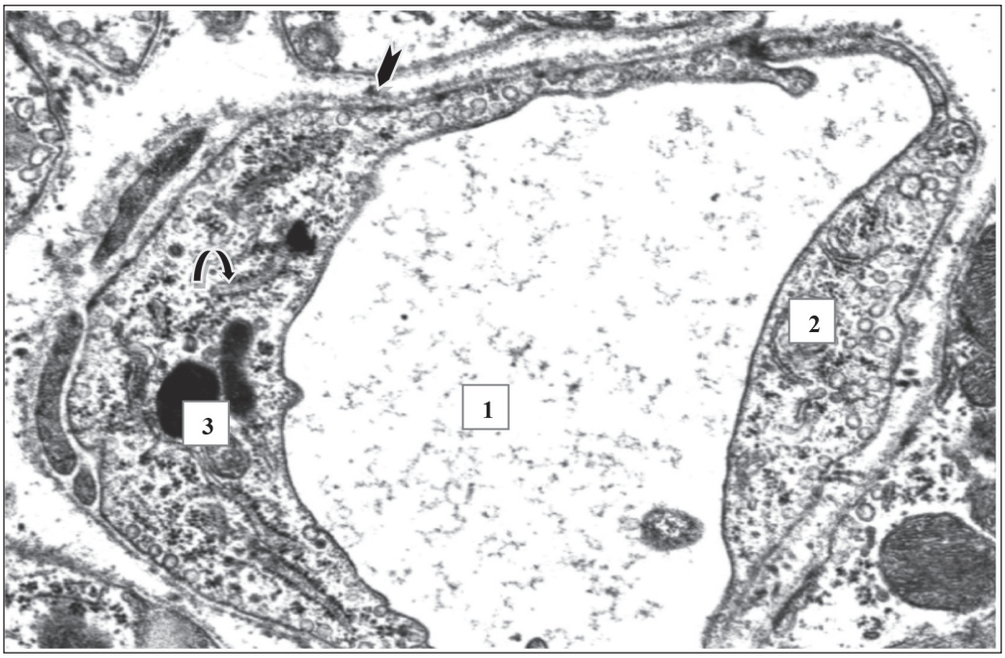


Fig.1. Blood capillaries of the left ventricle myocardium of rats with combined correction of congenital hypothyroidism by L-thyroxine and calcitonin. Electron microscopic photo. Magnification: 28000.
Lumen (1) of the capillary, mitochondria (2), Weibel–Palade bodies (3), ER tubules (⋂) in endothelial cells, basement membrane (◗).

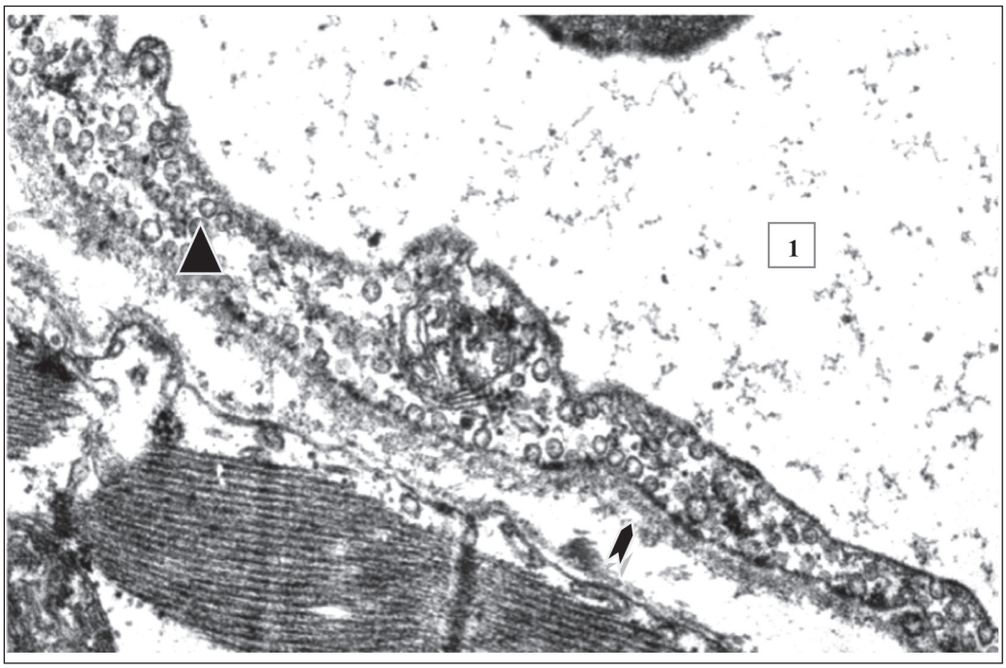


Fig.2. Blood capillaries of the left ventricle myocardium of rats with combined correction of congenital hypotireosis by L-thyroxine and calcitonin. Electron microscopic photo. Magnification: 40000.
Lumen (1) of the capillary, mitochondria (2), micropinocytotic vesicles (▲) in endothelial cells, basement membrane (◗).

DISCUSSION

It is known from the literature that in blood capillaries of the myocardium in sexually mature (100-day) rats with CHT destructive-dystrophic processes are approximately balanced with compensatory and adaptive ones. In the myocardium, the quantitative density of the capillaries decreases. Activation of transcytosis occurs against significant violations of vesiculation. Some of the endothelial cells of experimental animals contain a moderate amount of transport vesicles, while others

Table II. The morphometric indexes of MPV in endothelial cells of myocardial circulatory capillaries

Groups	Volumetric density, %	Quantitative density, 1/ μm³	Average area, 10^{-2} μm²	Form factor
Control	21,95±0,85	332,5±18,6	0,57±0,01	0,85±0,007
CHT	23,00±1,49	443,7±25,9*	0,55±0,01	0,84±0,006
CHT and correction	19,28±1, 19	307,6±32,7**	0,54±0,01	0,86±0,01

Note: * – p<0, 05 in comparison with the data of the Control;
** – p<0, 05 in comparison with the data of the group before treatment.

are overfilled with these structures and desquamate into the lumen [8].

The choice of pharmacological correction drugs for rats with congenital hypothyroidism was dictated by the fact that one of the reasons for the inefficiency of monotherapy with L-thyroxin may be the deficiency of calcitonin, a iodine-independent hormone of thyroid gland, whose content is lowered in blood plasma of patients with thyroidectomy [9]. The immune-enzyme analysis showed no significant difference in the plasma levels of free thyroxine in intact rats and rats with congenital hypothyroidism after complex substitution therapy (8.96 ± 1.39 pmol / l). The indicator is not significantly different from its value in intact animals of the same age and blood pressure.

In rats with congenital hypothyroidism, for which the drug L-thyroxin in combination with calcitonin was used, after the pharmacological correction, in general there is no apparent heteromorphism of the ultrastructure of the left ventricular myocardial blood capillaries, which was characteristic of animals without pharmacological correction. Capillaries in general maintain their integrity and have morphological features of functional activity similar to intact animals. Another feature in this observation group was the absence of apoptotic altered endothelial cells, which is obviously due to the ability of calcitonin to increase the activity of anti-apoptotic proteins in the cells [10].

CONCLUSIONS

In rats with congenital hypothyroidism, which have received L-thyroxine and calcitonin at birth, the myocardium capillaries generally remain intact and have morphological and functional signs of activity similar to intact animals, which is the theoretical basis for the need for calcitonin to be used in substitution therapy in hypothyroidism.

REFERENCES

1. Rastogi M. V., LaFranchi S. H. Congenital hypothyroidism. Orphanet J Rare Dis. 2010; 5: 17.
2. Katerhenchuk V.I., Beregova O.P. Cardiovascular hypothyroidism masks Internal Medicine. 2007; 3(3): 50-55.
3. Dernellis J., Panaretou M. Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. Am. Heart J. 2002;143(4):718-24.
4. Maksutina N. P., Pylypchuk L. V. Structured system of natural vitamins-antioxidants. Liki Ukr. 2002; 10: 31-34.
5. Parkhomenko A.N. Metabolic therapy, or cardioprotection in coronary heart disease: outcomes and perspectives. Cardiology. 2008; 4: 15-19.
6. Udovcic M, Pena RH, Patham B, Tabatabai L, Kansara A. Hypothyroidism and the Heart. Methodist Debakey Cardiovasc J. 2017;13(2):55-59.
7. Karupu V.Ya. Electron microscopy. K.: Vishcha School, 1984: 208 p.
8. Chuhray S. M., Lavrynenko V. E., Kaminsky R. F., Dzevulska I. V., Malikov O. V., Kovalchuk O. I., Sokurenko L. M. Morphofunctional status of cardio-vascular system of rats with congenital hypotireosis. Wiad Lek 2019; 72(2): 229-233.
9. Schulz R., Heusch G. Hibernating myocardium. Heart. 2000; 84(6): 587-594.
10. Sueur S., Pesant M, Rochette L, Connat J.L. Antiapoptotic effect of calcitonin gene-related peptide on oxidative stress-induced injury in H9c2 cardiomyocytes via the RAMP1/CRLR complex. J Mol Cell Cardiol. 2005; 39(6): 955-963.

Acknowledgements: The authors would like to thank the employees of the Scientific Research Institute Experimental And Clinical Medicine (Institute of Pathologists Problems) at Bogomolets National Medical University prof. L.O. Stechenko and T.P.Kuftyreva.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Liudmyla M. Sokurenko
Department of Histology and Embryology,
Bogomolets National Medical University
Kyiv, Ukraine
tel: +380675010815
e-mail: l-sokurenko@i.ua

Received: 01.03.2019
Accepted: 11.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

CLINICAL AND METABOLIC ANALYSIS OF DISORDERS IN PSORIATIC PATIENTS

Uljana Fedorova[1], Orysya Syzon[1], Igor Gajduchok[2], Kostjantyn Ischejkin[3], Marianna Dashko[1]
[1]DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE
[2]LVIV MEDICAL INSTITUTE, LVIV, UKRAINE
[3]UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

Introduction: Elucidation of the primary nature of biochemical shifts in psoriatic disease and prediction of interconnected subsequent changes in metabolic and inflammatory processes are important in foreseeing the dynamic development of pathological process and the choice of individual treatment.

The aim of the research was to assess the disorders and correlations between main indicators of protein, fat, hydrocarbon and pigment metabolism and specifics of inflammatory processes in psoriatic patients against the clinical course of dermatosis.

Materials and methods: We analysed the results of clinical and laboratory examinations conducted in 62 psoriatic patients. All these patients have been analysed as per their age, sex, prevalence and the type of skin rash as well as per the clinical disease form. Biochemical examinations were conducted using appropriate sets of reagents. To establish the possible correlation between the indicators of biochemical blood analysis, we calculated the correlation coefficient, which determines the nature of correlation between the studied variables.

Results: The analysis of results received upon examining psoriatic patients indicated that microbial-viral associations, stress factors and genetic predisposition were the most frequent trigger factors of psoriatic disease, which corresponds to the data from literary sources. We detected that the duration of psoriaric disease up to 5 years was the most common, and relapses were manifested in its limited form against the background of the disease advanced stage; the prevalent psoriasis was more common at the hospital stage. Our study justifies that metabolic changes occurred in the overwhelming majority of examined patients of different age groups. At that, abnormalities of a number of indicators of protein, lipid, hydrocarbon and enzyme metabolism have been established. In addition, the expressiveness of corresponding changes correlated with the prevalence of skin psoriatic process and the duration of dermatosis course as well as the presence of pathology of a number of internal organs, in particular of gastrointestinal tract, hepatobiliary and cardiovascular systems, that suggest the presence of systemic disorders at psoriasis.

Conclusions: The identification of independent mechanisms existing between some changes in metabolic process parameters in psoriasis has a theoretical and practical significance in dermatology, which involves the use of medications to regulate the detected disorders, the possibility to restore correlations, and it will inevitably contribute to the achievement of clinical and preventive effect.

KEY WORDS: psoriasis, metabolic disorders, hydrocarbon and pigment metabolism

Wiad Lek 2019, 72, 7, 1304-1309

INTRODUCTION

Psoriasis is a chronic polyetiologic papular and squamous dermatosis with a 64-72% share of genetic component. It is characterized by the uncontrolled, non-malignant hyperproliferation of epidermis, keratinisation disorders, inflammatory reaction in dermis, changes in various organs and systems [1]. This disease has been one of the most common in dermatological practice over the past decade. In particular, its ratio among other dermatoses types has reached up to 5%, and the number of patients in dermatological hospitals has increased up to 40% [1,2]. Nowadays it is relevant to study metabolic and inflammatory disorders and correlation interactions in psoriatic patients. The identification of mechanisms of some metabolic processes, especially lipid, protein, enzyme, carbohydrate metabolism as manifestation of functional insufficiency of the hepatobiliary system is valuable for understanding the pathogenesis of this dermatosis [2]. The elucidation of the primary nature of biochemical shifts in psoriatic disease and the prediction of interconnected subsequent changes in metabolic and inflammatory processes are important in the work of a practicing physician who may use them to foresee the dynamic development of pathological process and the choice of individual treatment for a patient [3,4].

THE AIM

The aim of the research was to assess the disorders and correlations between main indicators of protein, fat, hydrocarbon and pigment metabolism and specifics of inflammatory processes in psoriatic patients against the clinical course of dermatosis.

MATERIALS AND METHODS

We analysed the results of clinical and laboratory examinations of 62 psoriatic patients admitted to inpatient and outpatient treatment at Municipal Institution of Lviv Regional Council

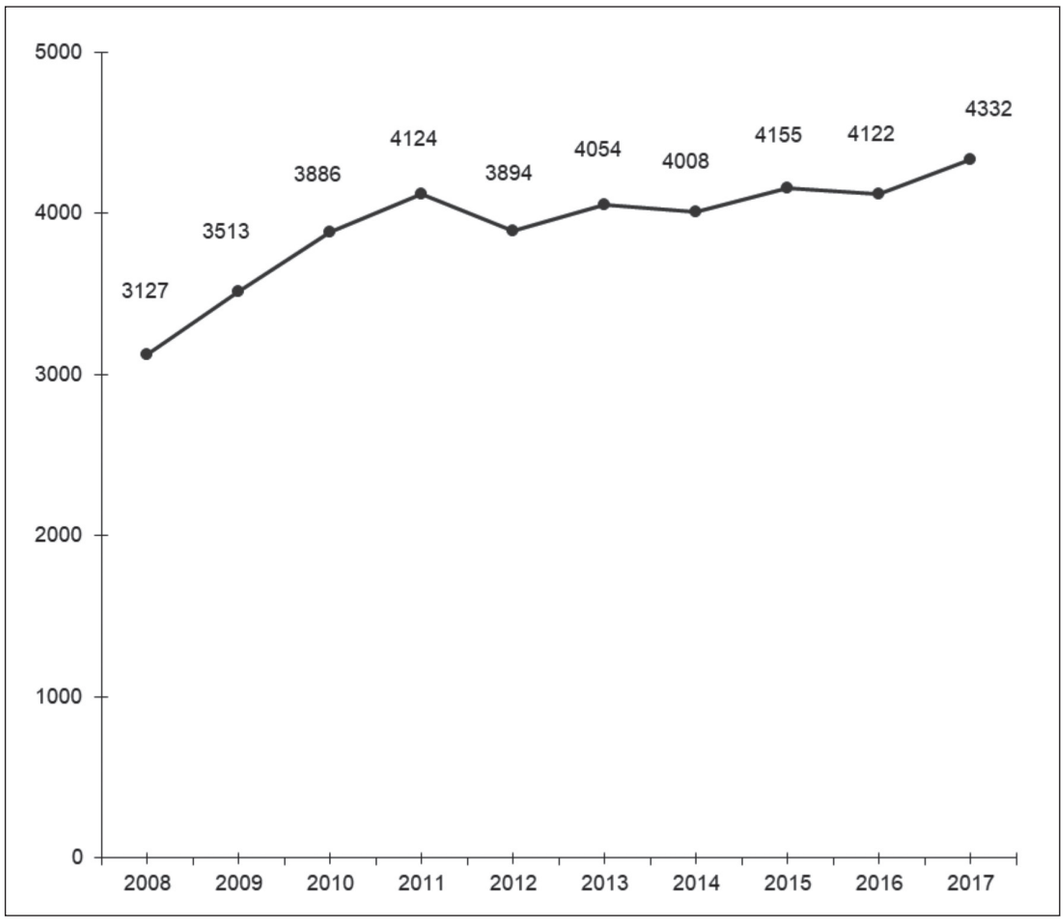


Fig. 1. Dynamics of psoriasis morbidity in Lviv region for the period of 2008-2017.

"Regional Clinical Skin and Venereal Diseases Dispensary" during 2015-2017. To assess the prevalence of skin psoriatic rashes, the PASI index (Psoriasis area and severity index) was applied. [5]. All patients have been examined according to their age, sex, prevalence and type of skin rash, as well as clinical form of the disease. To assess metabolic processes, we examined data on some parameters of protein, fat, hydrocarbon and pigment metabolism. Biochemical studies were performed by applying automated closed method, and using a biochemical analyzer and a set of appropriate reagents on a photoelectric colorimeter KFK-2 manufactured by Zaghorsky opto-mechanical plant (PA "ZOMZ", Ukraine). KFK-2 is intended to measure wavelength ranging from 315 to 980 nm separated by light filters specific for their transmittance ratio (from 100% to 5%) and optical density (from 0 to 1.3) in liquid solutions and solids, as well as to determine the concentration of substances in solutions by plotting calibration graphs. A 6.3 V, 15 W incandescent lamp was used as a light source in a colorimeter. Light energy was absorbed by photocells F–2A working in a 315-540 nm spectral region and FD–24K working in a 550-980 nm spectral region. Optical system is a single-beam one. The following biochemical parameters were measured: total protein, activity of liver transaminases – using a set of reagents (SIMKO Ukraine), and the activity of amylase, thymol test, total lipids, triglycerides, beta-lipoproteins, urea, bilirubin – using reagents ("BIO -Lachema ", Czech Republic). Seromucoids were detected in blood serum using the nephlometric method (Mefan 8001, Ukraine), proteinogram – using the method of electrophoresis with application of gel-foreometer and reagents ("AVGE-2", Ukraine). The results of the research were analyzed using the IBM SPSS Statistics v.21 statistical package. The probability of discrepancies between the samples was estimated according to Student's t-criterion, the differences were considered as probable at $p < 0.05$. Correlation analysis was performed by means of Pearson correlation coefficient, applying the method of logistic regression. The study of patients was conducted in accordance with the 7th revision of the principles of the Declaration of Helsinki (2013), the European Convention on Human Rights and Biomedicine, and the relevant laws of Ukraine. All the patients gave their personal consent in a written form to participate in this research. The control group consisted of 20 apparently healthy individuals of the corresponding age and sex.

RESULTS

When analyzing the retrospective data, it is obvious from Figure 1 that since 2008 the number of registered psoriatic cases in Lviv region has increased from 3127 (2008) to 4332 (2017), as can be observed in Fig. 1. The dynamics of newly diagnosed psoriasis cases has increased by 29.6%.

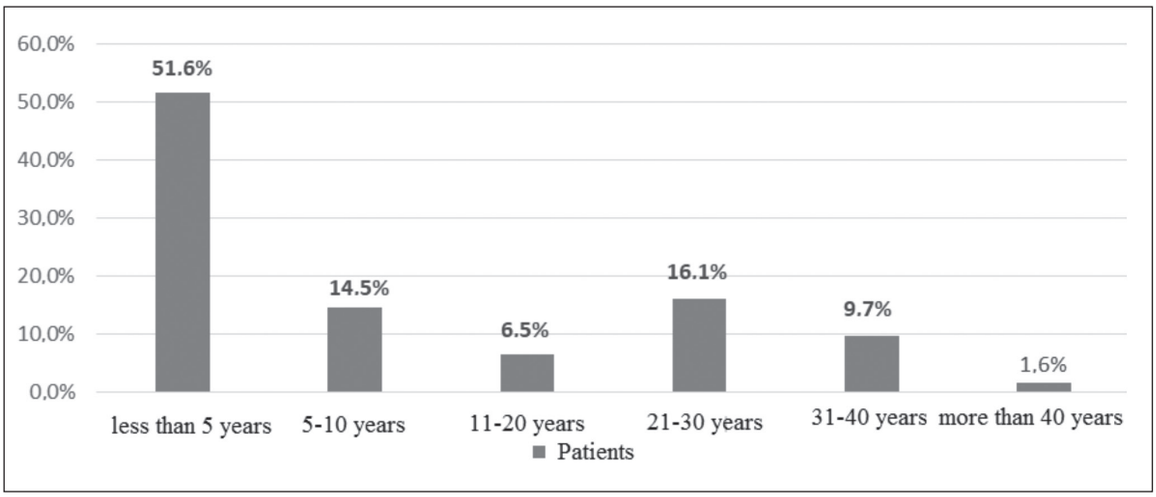


Fig. 2. The dynamics of psoriasis in Lviv region for the period of 2008-2017.

All patients were thoroughly studied in respect of their medical histories and clinical examinations. As a result, it was found that in 10 (17.5%) patients a genetically predetermined psoriatic disease was detected as well as factors that preceded the primary onset of skin disease manifestations. In particular, microbial-viral factor was found in 13 (21.0%) patients, stressful situations – in 12 (19.4%) cases, alcohol abuse – in 9 (14.5%), endocrine disorders – in 2 (3.22%), occupational hazards – 2 (3.22%), injury – 1 (0.61%). Thirteen (21.0%) patients did not register causative factors of the disease onset.

Figure 2 indicates the duration of psoriatic disease in the examined patients.

As can be observed from Figure 2, the disease duration in the examined patients ranges from 3 months to 40 years or longer. Based on the data obtained, the most commonly registered cases of psoriasis duration are up to 5 years – 32 (51.6%) patients.

In our study, all patients were analyzed in respect to the disease grade as well as the type of rashes prevalence. The limited type of psoriasis accompanied by advanced grade was diagnosed more frequently than the hospital one (85.7% vs. 14.3%, $P < 0.01$). The hospital disease grade was dominant for the prevalent type (75.7%, $P< 0.05$).

In 48 (77.42%) patients the disease course was characterized by a tendency to frequent acute conditions. The mild form of psoriatic process was observed in 3 (4.84%) patients, moderate severity – in 50 (80.6%) patients, and severe grade – in 9 (14.5%) patients. In 24 (38.7%) patients no sustained remission was observed.

Consequently, in the context of the above, it can be stated that microbial-viral associations, stress factors and genetic predisposition were the most frequent trigger agents of psoriatic disease, which corresponds to the data from literary sources [6, 7, 8]. Psoriasis with duration of the disease up to 5 years old with recurrent course and average severity of illness was registered more often, with a limited form – in the progressive stage, and with spreading from – in the hospital stage. The prevalent psoriasis was more common for the hospital grade. These data show some regional peculiarities concerning our patients and possible epigenetic effects specific for this region as compared to the data provided by our colleagues [9, 10, 11].

The severity of changes in the parameters of the studied metabolic processes directly depended on the duration, activity of psoriasis, the presence of comorbid pathology and differed from that of practically healthy persons. A significant reduction in the content of total protein (1.2 times; $P< 0.05$) and blood serum albumin (1.3 times; $P< 0.05$), an increase in the percentage of α2- (1.2 times; $P< 0.05$) and γ-globulins (1.3 times; $P< 0.05$) has been established, which may be due to the hyper-production of inflammation. Increase in serum uric acid level is caused by the excessive inflammation of epithelium, synovial fluid. We have observed an increase in the activity of ALT (1.8 times; $P< 0.05$), AST (1.7; $P< 0.05$), and amylase (1.3 times; $P< 0.05$).

The disruption of pigment exchange was characterized by an increase in the activity of the thymol test (2.0 times; $P <0.01$) and the level of bilirubin (1.5 times; $P <0.05$). The changes in lipid metabolism in patients with psoriasis are indicated by an increase in the concentration of triglycerides (1.8 times; $P <0.05$), cholesterol (1.2 times; $P <0.05$).

General increase in seromucoids (2 times; $P< 0.15$) may indicate the damage of connective tissues. In psoriatic patients suffering from joint damages, in 60.1% of cases the inflammatory, cholecystophobic and dyslipidemic syndromes were confirmed.

In order to better understand the role of metabolic processes related to psoriatic disease, we have carried out a correlation analysis of the detected changes in metabolic and inflammatory processes in psoriatic patients.

In the course of this study, we have detected correlations between changes in some biochemical parameters and the presence of pathology of a number of internal organs, in particular of gastrointestinal tract, hepatobiliary and cardiovascular systems, that suggest the presence of systemic

Table I. Correlation of some biochemical parameters with the development of inflammatory syndrome in patients with psoriatic disease

Factors	r	P
Seromucoids	+0.52	< 0.05
Beta-lipoproteins	+0.52	< 0.05
Alfa2- globulins	+0.44	< 0.05
Beta2-globulins	+0.43	< 0.05
Albumin	-0.77	< 0.01

disorders at psoriasis, with their peculiarities for different stages of this disease.

Thus, correlation between the levels of bilirubin and total lipids (r = +0.54) and alpha-1 globulins (r = +0.37) and amylase (r = +0.45) has been identified. The thymol test manifested a strongly expressed inverse correlation with seromucoids (r = -0.85), a weaker one – with AlAT (r = +0.67); with glucose (r=+0.50) and inverse beta lipoproteins (r = -0.50, weakly expressed correlation with triglycerides (r = +0.39), albumins (r = –0.39) and AsAT (r = +0.43). The total protein slightly correlated with the urea level (r = +0.48), gamma globulins (r = +0.39) and albumins (r = +0.36). Glucose expressively correlated with the ALT level (r = + 0.60), weaker – with seromucoids (r = +0.47), triglycerides (r = +0.40), beta lipoproteins (r = +0.38) and AST (r = +0.35). The level of beta-lipoproteins demonstrated a strong correlation between seromucoids (r = +0.71), a weaker one – with triglycerides (r = +0.54), beta-globulins (r = +0.51) and albumins (r = +0.50). Also, weak correlations with alpha-2 globulins (r = +0.49), gamma globulins (r = +0.47) and AST (r = +0.46) have been noted. The level of total lipids correlated with triglycerides (r = +0.55) and weakly with albumin (r = +0.46) and alpha-2 globulins (r = +0.40). The level of triglycerides expressively correlated with the level of albumin (r = +0.70) and seromucoids (r = +0.56) while it weakly correlated with gamma globulins (r = +0.41), and alpha -2 globulins (r = +0.38). The level of albumin demonstrated an inverse correlation with the level of alpha-1 globulins (r = -0.57) and direct correlation with seromucoids (+0.52), as well as an inverse weak correlation with gamma globulins (r = –0.43) and urea (r = +0.36). Alpha-1 globulins correlated with AST (r = +0.53) and weakly correlated with the urea level (r = +0.43). Alpha-2 globulins demonstrated expressed correlations with gamma-globulin levels (r = +0.63) and urea (r = +0.52). Beta globulins showed a weak correlation with AST (r = +0.49). Gamma globulins demonstrated a weak correlation with the urea level (r = +0.44), seromucoids (r = + 0.42) and AST (r = +0.38). The ALT level slightly correlated with the AST (r = +0.46) and seromucoid level (r = + 0.41). At the same time, AST showed an expressed correlation with the level of seromucoids (r = +0.60).

At psoriatic disease, depending on its stage and according to our observations, indicators of thymol test, seromucoids, β-lipoproteins, transaminases were the first and foremost to correlatively react. In psoriatic patients, a strong inverse correlation between the indicators of thymol test and blood serum seromucoids (r = -0.8) has been proven, and at the advanced dermatosis stage it manifests the most expressively (r = -0.92), which emphasizes the highest activity of metabolic processes. The correlation between the thymol test indices and AlAT activity is strong and direct (r = +0.75). In the course of disease development, initially increases the index of AlAT, and then, when the process becomes preserved – AsAT. In addition, the AlAT activity inversely correlates with the glucose concentration (r = -0.6), which indicates the activation of gluconeogenesis due to liver failure and subsequently it becomes an initiating factor in the development of diabetes mellitus. These correlations are regular since advancing of the psoriatic process is accompanied by the activation of a metabolic response and preservation of the metabolic deficiency over the time.

The level of thymol test is most sensitive to functional changes in the hepatobiliary system and synchronously increases with transaminases as indicators of hepatic-cellular deficiency. In addition, there is evidence that thymol test indices change sooner than other indicators of biochemical examination and clinical signs of liver damage as a manifestation of mesenchymal-inflammatory syndrome. In our opinion, the reactivity of thymol test towards its increase is due to a parallel decrease in seromucoid indicators and β-lipoprotein parameters, the sets of which demonstrate autoimmune properties and cause the activation of connective tissue disruption and the development of psoriatic disease in the form of collagenosis.

The levels of serum seromucoids and β-lipoproteins demonstratesa one-vector strong correlation (r = +0.71), regardless of the psoriatic process stage. We assume the possibility of formation of their complexes with obtaining autoimmune properties, and the development of pathological process per the autoimmune type. At the same time, conspicuous is the fact that the inverse correlation between the seromucoids level and the concentration of serum triglycerides (r = -0.6) as well as seromucoids and the activity of AsAT (r = -0.60), especially at the hospital stage of dermatosis, indicates the activation of lipid, enzyme exchange in the hepatobiliary system.

Particularly interesting were the correlations of inflammatory processes development in patients with psoriasis, established by the method of logistic regression with seromucoids (r = +0.61), beta-lipoproteins (r = +0.59), alpha2-globulins (r = +0.51), albumin (r = -0.48), beta2-globulins (r = +0.47) – which allows predicting inflammatory processes in these patients (Table I). The constant b_0 = -56.456.

Correlations appeared on the basis of logistic regression between the syndrome of metabolic disorders and albumin (r = -0.54), triglycerides (r = + 0.50), total lipids (r = +0.49, bilirubin (r = +0.51), uric acid (r = +0.47) also turned to be important, and can be used to characterize the combination of metabolism disorders in patients with psoriasis (Table II). The constant b_0 = - 446.930.

Table II. Correlations some biochemical parameters with the development of syndrome of metabolic disorders in patients with psoriatic disease

Factors	r	P
Albumin	-0.54	< 0.05
Triglycerides	+0.50	< 0.05
Cholesterol	+0.49	< 0.05
Bilirubin	+0.51	< 0.05
Uric acid	+0.47	< 0.05

DISCUSSION

Thus, when analysing the correlations of biochemical parameters, it is possible to make certain conclusions: the indices of serum albumin content in psoriatic patients showed a unidirectional average correlation with the level of serum seromucoids. This fact indicates the inhibition of protein synthesis by liver cells caused by the immune response of reticuloendothelial tissue to priming factors (toxins, drugs, infections) that activate the interaction of seromucoids and β-lipoproteins and promote the formation of immune complexes thus creating conditions for the immune inflammation. An additional confirmation of the described, there is a multi-vector expressed correlation between the content of albumins and a1-globulins and one-vector correlation between a_2- and γ-globulins of blood serum of psoriatic patients, which allows us to verify the presence of cellular liver deficiency. Urea as a decay product of purine bases directly correlated with the level of a_2-globulins, and may also create conditions for immune-inflammatory processes [13]. We have identified a significant correlation between albumin and triglyceride content, direct average correlation between albumins and β-lipoproteins; β-globulins and β-lipoproteins, which explain the disorder in relationship of protein synthesizing and lipid liver disfunction [14]. The traced correlation between triglyceride and β-lipoprotein indices, the content of total lipids indicate the possibility of their interaction and may ultimately lead to significant dyslipidemia as signs of metabolic syndromes [14]. Besides, the dependence of total lipid levels and the concentration of serum bilirubin in psoriatic patients is observed indicating the correlation between a disorder of the lipid and pigment-forming function of the hepatobiliary system. An increased triglycerides level leads to an increased level of albumins and serum seromucoids indicating the immune-inflammatory and compensatory detoxification components in psoriatic patients in the context of lipid metabolism disorder occurred due to the conversion of carbohydrates into lipids [15]. An inverse correlation between the level of albumins and alpha-1 globulins suggests an additional protective clearance function of albumins accompanied with inflammatory disorders that affects the growth of seromucoids [16]. The increased beta-2 globulin levels correlate with the growth of alpha-2 globulins and urea, which can lead to an increase in auto-aggression and abnormal protein metabolism [17]. The increased AsAT level leads to increased serum seromucoid levels accompanied by the autoimmune damage of connective tissue and possible development of arthropathies [18]. Weak correlations of different nature have been detected among other biochemical parameters of blood serum of psoriatic patients, which prevents the establishment of regularities and indicates the multimodality and complexity of metabolic disorders occurred at this disease.

The elucidation of mechanisms of some metabolic processes, in particular lipid, protein, enzyme, carbohydrate metabolism and inflammatory parameters allowed to deepen our understanding of their role in the pathogenesis of this dermatosis.

The expressiveness of changes in biochemical parameters correlated with the prevalence of the skin psoriasis and the duration of the course of dermatosis, as well as the presence of a pathology of a number of internal organs, in particular those of hepatobiliary, pancreatic and cardiovascular systems, indicate systemic disorders at psoriasis.

The identification of independent mechanisms between the studied changes in the parameters of metabolic processes at psoriasis has theoretical and practical significance in dermatology, which involves the use of drugs for regulating the established disorders, the possibility of restoring correlations, which will contribute to the achievement of the clinical and preventive effect. Metabolic and inflammatory shifts at psoriatic disease and prediction of their interconnected changes in the metabolic rate are important in predicting the dynamic development of the pathological process, the choice of personified treatment of the patient.

CONCLUSIONS

1. Most often the following features of psoriatic disease were revealed in Lviv region: trigger factors – infectious – 21.0%, stress – 19.4%, genetic factors -17.5%; clinical – limited type with a progressive stage – 85.7%, common type in the hospital stage – 45.2%, with a dominant average severity – 80.6%, and often a relapsing course – 77.2%.
2. In patients with psoriatic disease, in comparison with healthy people, manifestations of inflammatory disorders with an increase in levels of alpha-2 globulins (1.2 times), seromucoids (2.0 times); disruption of protein metabolism – uric acid (2.3 times), total protein (2.0 times); pigment exchange – thymol test (2.0 times) and bilirubin (1.5 times); enzyme metabolism of the liver – ALT (1.8 times), AsAT (1.7 times); lipid metabolism – cholesterol (1.2 times), triglycerides (1.8 times) have been identified.
3. On the basis of the logistic regression method, correlations of the development of inflammatory processes in patients with psoriasis with the levels of seromucoids (r = +0.61), beta-lipoproteins (r = +0.59), alpha2-globulins (r = +0.51) , albumin (r = -0.48), beta2-globulins (r = +0.47), as well as between metabolic syndrome and albumin levels (r = -0.54), triglycerides (r = + 0.50),

cholesterol (r = +0.49), bilirubin (r = +0.51), uric acid (r = +0.47) have been established, which characterize the disruption of protein, lipid, carbohydrate, pigment metabolism in these patients, requiring a personified approach to their therapy, on the background of cytotoxic treatment.

REFERENCES

1. Griffiths C. E., Walt J. M., Ashcroft D. M., Flohr C., Naldi L., Nijsten T., Augustin M. The global state of psoriasis disease epidemiology: a workshop report. Br. J. Dermatol. 2017;177(1):4-7.
2. Ng C. Y., Tzeng I. S., Liu S. H., Chang Y. C., Huang Y. H. Metabolic parameters in psoriatic patients treated with interleukin-12/23 blockade (ustekinumab). J Dermatol. 2018; 45(3):309-313.
3. Radtke M. A., Mrowietz U., Feuerhahn J., Härter M., Kiedrowski R., Nast, A., Augustin M. Early detection of comorbidity in psoriasis: recommendations of the National Conference on Healthcare in Psoriasis. JDDG: J. Deut. Dermatol.2015;13(7):674-689.
4. Syzon O. O., Stepanenko V. I. Diagnosis and treatment of arthropathic psoriasis, taking into account data on pathogenesis and peculiarities of the clinical course of dermatoses. Ukr. Zhur. Dermat. Vener. Kosmet. 2016;2:13-26. (In Ukrainian)
5. Raychaudhuri S. K., Maverakis E., Raychaudhuri S. P. Diagnosis and classification of psoriasis. Autoimmun. Rev. 2014;13(4-5):490-495.
6. Boehncke W. H. Etiology and pathogenesis of psoriasis. Rheum. Dis. Clin. 2015;41(4):665-675.
7. Syzon O. O., Stepanenko V. I. Control over the development and course of concomitant pathology in patients with arthropathic psoriasis. Ukr. Zhur. Dermat. Vener. Kosmet. 2014;2:13-24. (In Ukrainian).
8. Hawkes J. E., Chan T. C., Krueger J. G. Psoriasis pathogenesis and the development of novel targeted immune therapies. J. Allerg. Clin. Immunol. 2017;140(3):645-653.
9. Chandra A., Ray A., Senapati S., Chatterjee R. Genetic and epigenetic basis of psoriasis pathogenesis. Mol. Immunol. 2015;64(2):313-323.
10. O'Rielly D. D., Rahman P. Genetic, epigenetic and pharmacogenetic aspects of psoriasis and psoriatic arthritis. Rheum. Dis. Clin. 2015;41(4):623-642.
11. Pollock R. A., Abji F., Gladman D. D. Epigenetics of psoriatic disease: a systematic review and critical appraisal. J. Autoimmun. 2017;78:29-38.
12. Mahil S. K., Capon F., Barker J. N. Genetics of psoriasis. Dermatol. Clin. 2015;33(1):1-11.
13. Sheikh G., Masood Q., Majeed S., Hassan I. Comparison of levels of serum copper, zinc, albumin, globulin and alkaline phosphatase in psoriatic patients and controls: A hospital based casecontrol study. Ind. Derm. O. J. 2015;6(2):81-83.
14. HajHeydari Z.. Serum lipids and lipoproteins in patients with psoriasis. Arch. Iran. Med. 2014;17(5):343-347.
15. Nakhwa Y. C., Rashmi R., Basavaraj K. H. Dyslipidemia in psoriasis: A case controlled study. Int. Sch. Res. Notices. 2014;7(3):87-92.
16. Işik S., Kılıç S., Öğretmen Z., Çakır D. Ü., Türkön H., Cevizci S., Hız M. M. The correlation between the psoriasis area severity index and ischemia-modified albumin, mean platelet volume levels in patients with psoriasis. Adv. Dermat. Allerg. 2016;33(4):290-293.
17. Moorchung N., Vasudevan B., Kumar S. D., Muralidhar A.. Expression of apoptosis regulating proteins p53 and bcl-2 in psoriasis. Ind. J. Path. Micro. 2015;58(4):423-427.
18. Gladman D. D. Historical Perspectives on Psoriatic Arthritis. In: Psoriatic Arthritis and Psoriasis. Springer Cham 2016;3-6.

Acknowledgments: We are very grateful to the staff of biochemical laboratory of Lviv Regional Skin and Venereal Dispensary and the Center of Biostatistics of Danylo Halytsky Lviv National Medical University for their assistance in carrying out this research.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Uljana Fedorova
Danylo Halytsky Lviv National Medical University
Lviv, Ukraine
e-mail: fedorovauljana89@gmail.com.

Received: 23.02.2019
Accepted: 10.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

GENERAL IMMUNOLOGICAL REACTIVITY OF PATIENT'S ORGANISM WITH CHRONIC HEPATITIS C

Iryna V. Balaniuk, Elena V. Myronyk, Yuriy O. Randiuk, Andriy V. Andruschak
HIGHER EDUCATIONAL STATE INSTITUTION OF UKRAINE «BUKOVYNIAN STATE MEDICAL UNIVERSITY», CHERNIVTSI, UKRAINE

ABSTRACT

Introduction: Nowadays, the number of chronic carriers of hepatitis C virus (HCV) is considered to be from around 150 to 500 million by the most of infectionists and epidemiologists. Being one of the most dangerous diseases of the liver of viral etiology hepatitis C increases annually.

The aim: To determine the level of general immunological reactivity of patients with chronic hepatitis C.

Materials and methods: This study does not contradict the principles of the Helsinki Declaration (2013), the European Convention on Human Rights and Biomedicine.
A clinical and laboratory examination of 31 patients with chronic hepatitis C was conducted during 2014-2015 on the basis of the infectious department of Chernivtsi Regional Clinical

Results: The initial condition of clinical and laboratory examination of patients with chronic hepatitis C is normally considered to be a clinical examination of each patient and first of all hemograms where absolute and relative number of major populations of immunocompetent cells, platelets, erythrocytes and erythrocyte sedimentation rates (ESR) were determined.

Conclusions: General immunological reactivity in patients with chronic hepatitis C increased to
30,07% and the factors activation and mechanisms of nonspecific anti-infection protection decreased that create a condition for prolonged persistence of hepatitis C virus and the progression of a chronic infectious process in patients' organism.

KEY WORDS: Chronic hepatitis C, immunological reactivity of organism

Wiad Lek 2019, 72, 7, 1310-1314

INTRODUCTION

Viral hepatitis is a kind of pathology within the system «macroorganism-causative agent», and persistency of generally biological phenomena, the mechanism of which is in a direct relation to such cardinal problems of modern medicine as cancerogenesis, chronic infections, congenital developmental defects and others. Despite numerous literary sources available concerning viral hepatitis there are a lot of contradictions promoting further study of the relationships in the "virus-cell" system, the persistence of the virus and the response to its immune system. There is a high demand to elaborate the universal system of controlling diseases within the framework of a comprehensive program to fight infections as (hepatitis B and C) known as *blood-borne* infections. Hence there is the need to characterize a *causative agent*, pathogenesis of diseases, cell manifestation, diagnostics, and therapeutic prophylaxis [1].

The occurrence of viral hepatitis can`t be explained by only infection of the liver cells by hepatitis C virus (HCV), that is characterized by a high level of tropism and aggressiveness (virulence). The important condition for the progression of the disease, except for direct contact with the "virus-cell" system, is the presence of a specific immunological precondition, first of all autoimmune restructuring at the early stages of infection [2]. This conception is evidenced by the well-known fact of so-called "healthy carrier" when virus infection is present in the organism though the infectious process does not reach its highest manifestation in order to be qualified as a disease by a clinician. One should emphasize that pathogenesis and hepatitis C clinic are determined by the state of factors and mechanisms of nonspecific anti-infection protection mostly and the condition of the human immune system meaning a real possibility of transformation of the process into a chronic one and a life-long persistence of HCV. [3].

In addition, the severity of the disease course and favourable conditions of any illness prediction depend on the degree of intoxication as well as the adequacy of the immunological reactivity of the patient's organism. [4].

THE AIM

To determine the level of general immunological reactivity of patients with chronic hepatitis C.

MATERIALS AND METHODS

This study does not contradict the principles of the Helsinki Declaration (2013), the European Convention on Human Rights and Biomedicine.

A clinical and laboratory examination of 31 patients with chronic hepatitis C was conducted during 2014-2015 on the

basis of the infectious department of Chernivtsi Regional Clinical Hospital with certain paraclinical techniques being included. The research comprised patients of both sexes (21 males and 10 females), at the age of 26-63 years who were treated in the hospital. The average age of the examined patients was 44.55 ± 1.14 years. Among them, 15 (48.39%) were older than the middle age, and 16 (51.61%) younger than that one. The control group consisted of 30 practically healthy individuals (21 (70%) male patients and 9 women), at the age of 46.81 ± 2.41years. 21 patients had «chronic hepatitis C genotype of hepatitis C virus (HCV) that is 1b, without liver disorders, 7 patients with chronic hepatitis C, genotype HCV 1b, with liver disorders», 2 patients with «chronic hepatitis C, genotype HCV 3a, without liver disorders» and one patient with «chronic hepatitis C, genotype HCV 3b without liver disorders». 24 (77,42%) patients with chronic hepatitis C had their disease course without any liver disorders. The whole blood was taken from all the patients with chronic hepatitis C and practically healthy individuals for studying the level of immunological reactivity of the patients` organism which was displaced in a clean tube with EDTA anticoagulant - K2 * 2 H2O, without damage of the structure of leukocytes, red blood cells and prevents platelets aggregation. The test tubes were carefully shaken, 5-10 times to a good complete mixing. The automatic hematological analyzer of the HB series was used for calculation of blood elements of the peripheral blood and their analysis. The absolute and relative number of the main populations of immunocompetent cells was calculated according to the recommendations contained in the analyzer`s manual.

Based on the obtained results of absolute and relative number of the main populations of immunocompetent cells the immune-hepatological indicators were found, which determined general immunological reactivity of the patients` organism with hepatitis C. The obtained digital data were statistically processed by the variational calculations with the authenticity of the difference of signs determination by Student criterion, with mean values (M) and standard error (± m) usage, Student criterion (t) and probability index (P). P<0,05 was considered to be the reliable one. The statistical calculation was carried out on the IBM Pentium-IV computer, by the Microsoft Excel Professional for Windows XP package and Stat Plus Professional 2009 program.

RESULTS AND DISCUSSION

The initial condition of clinical and laboratory examination of patients with chronic hepatitis C is normally con-

Table I. Absolute and relative amount of major populations of immunocompetent cells of patients' peripheral blood with chronic hepatitis C

Populations of immunocompetent cells	Measure units	Patients with chronic hepatitis C (n=31) M±m	Practically healthy individuals (n=30) M±m	Degree of immune disorders	P
Agranulocytes	%	29,91±0,31	32,36±1,18	-I	<0,05
	kh·10^9/l	1,23±0,07	1,58±0,17	-I	>0,05
Leucocytes	%	26,35±0,25	27,50±0,91	-I	>0,05
	kh·10^9/l	1,08±0,03	1,34±0,17	-I	>0,05
Monocytes	%	3,55±0,05	4,86±0,45	-I	<0,05
	kh10^9/l	0,15±0,01	0,24±0,02	-II	<0,05
Granulocytes	%	70,09±0,73	64,86±1,81	+I	<0,05
	kh·10^9/l	2,88±0,12	3,17±0,32	-I	>0,05
Neutrophil Granulocytes	%	68,19±0,67	62,63±1,61	+I	<0,05
	kh·10^9/l	2,80±0,11	3,06±0,30	-I	>0,05
Segment nucleus Neutrophils	%	64,45±0,61	59,53±2,89	+I	>0,05
	kh·10^9/l	2,65±0,10	2,91±0,31	-I	>0,05
Stabs Neutrophils	%	3,74±0,11	3,10±0,52	+I	>0,05
	kh·10^9/l	0,15±0,07	0,15±0,02	-	-
Eosinophil Granulocytes	%	1,90±0,10	2,23±0,17	-I	>0,05
Leucocytes	kh·10^9/l	4,11±0,27	4,88±0,97	-I	>0,05
Platelets	kh·10^9/l	168,17±10,09	202,37±2,02	-I	<0,05
Erythrocytes	kh·10^{12}/l	4,34±0,45	4,73±1,01	-I	>0,05
Hemoglobin (Hb)	gramme/l	137,58±11,17	121,75±2,17	+I	>0,05
Increase of erythrocyte sedimentation rate	mm/ year	10,52±0,77	6,08±0,31	+III	< 0,01
Avarage patients'age	years	44,55±1,14	46,21±2,41	-	> 0,05

Table II. General immunological reactivity of patients' organism with chronic hepatitis C

I Imuno-haematological indices	Measure units	patients with chronic hepatitis C (n=31) M±m	practically healthy individuals (n=30) M±m	Degree of immune disorders	R
Index of immunological reactivity of organism	C.U.	7,96±031	6,12±0,15	+I	<0,01
Index of heterospecific reactivity	C.U.	40,90±0,43	43,30±069	-I	<0,01
leucocyte - granulocyte index	C.U.	3,76±0,19	4,09±0,17	-I	>0,05
lymphocyte index	C.U.	0,39±0,04	0,42±0,04	-I	>0,05
Index of leucocytes' change	C.U.	2,34±0,17	2,08±0,16	+I	>0,05
leucocyte index	C.U.	1,66±0,10	1,47±0,07	+I	>0,05
Idex of Allergy	C.U.	0,77±0,15	0,77±0,17	-	>0,05
Correlation index of lymphocytes and monocytes	C.U.	7,43±0,29	6,95±0,27	+I	>0,05
Correlation index lymphocytes and eosinophils	C.U.	13,87±0,27	16,55±0,17	-I	<0,01
Correlation index of eosinophils and lymphocytes	C.U.	0,071±0,005	0,080±0,005	+I	>0,05
Neutrophil- lymphocyte coefficient	C.U.	2,59±0,18	2,38±0,17	+I	>0,05
Correlation index of neutrophils and monocytes	C.U.	19,21±0,27	16,56±0,42	+I	<0,01
Index of correlation of agranulocytes and ESR	C.U.	2,84±0,21	4,41±0,27	-II	<0,05
Index of correlation of agranulocytes and ESR	C.U.	0,39±0,04	0,63±0,043	-II	<0,05

sidered to be a clinical examination of each patient [5,6] and first of all hemograms where absolute and relative number of major populations of immunocompetent cells, platelets, erythrocytes and erythrocyte sedimentation rates (ESR) were determined (Table I).

A relative number of granulocytic leukocytes grows at a rate of 8,06 % in patients with chronic hepatitis C, though their absolute number tends to decrease by 9.29%. The growth of the relative number of granulocytic leukocytes is due to the increase of the relative number of neutrophilic granulocytes at a rate of 8,88 %, and the rate of the erythrocyte sedimentation rate up significantly by 73,03 % (P <0,01). The data indicated below are indicative of inflammatory process in patients with chronic hepatitis C. Non-specific factors and mechanisms of anti-infection protection response to inflammation, and first of all granulocytic leukocytes: neutrophil granulocytes including their subpopulation - segmental neutrophils (an increase in the relative amount of 8.26%), stab nucleus neutrophils (an increase in the relative amount of 20.65%). The relative number of eosinophilic granulocytes is reduced by 17.37%. On the background of relative number of granulocytic leukocytes growth (all subpopulations of neutrophilic granulocytes) the absolute amount of these leukocyte forms tended to decrease by 10.07%, general type of neutrophil granulocytes - by 9.29%, segmental neutrophils - by 9.8%. The absolute amount of platelets was decreasing by 20.34% in addition. The agranulocyte population of leukocytes (leukocytes, monocytes and macrophages) in patients with hepatitis C was changed due to the relative amount of agranulocytes at the rate of 8.19% decrease, absolute (by 60%) and relative (by 36.90%) amount of monocytes / macrophages, and the absolute number of lymphocytes tended to decrease (by 24,07 %). The changes in the absolute and relative number of granulocytic and agranulocytic forms of polynuclear, mononuclear leukocytes and lymphocytes are given in the research, they are also indicative of inflammatory reaction and endogenous intoxication and in case the fight against it the polymorphonuclear granulocytes prevail. The changes of the absolute and relative number of major populations of immunocompetent cells are also shown in the research affecting general immunological reactivity of the patients` organism with chronic hepatitis C. The results of immunological

reactivity of the patients` organism with chronic hepatitis C can be seen in Table II.

Contents of the absolute and relative number of major populations of immunocompetent cells are indicative of activation and adequate response of the factors and mechanisms of inborn immunity to the causative agent and the processes caused by it when interacting with hepatocytes, netrophils, B-lymphocytes and monocytes macrophages. The inborn and specific acquired immunity is known to tightly interact and significantly complement each other. The determination of immune-hematological indicators, which characterize the immunological reactivity of the patients` organism with chronic hepatitis C, showed the increase of immune reactivity of the patients` organism with chronic hepatitis C of 30.07%. The tendency of the lymphocytic index decrease at the rate of 7,69 % reflects the notion of humoral response and predominance of cellular immune response and the growth of the neutrophils and monocytes ratio indicates the advantage in anti-infective protection of the patients` body with chronic hepatitis C of the microphage protective system over the macrophage one. The ratio index decrease of the relative number of lymphocytes and eosinophils to 19,32 % and the increase to 18.33% ratio of eosinophils and lymphocytes shows the predominance of delayed type hypersensitivity over the one of an immediate type. This is confirmed by the invariability of the allergy index. The insignificant (P> 0,05) increase of the lymphocytes and monocytes ratio index (6.91%) is indicative of an affector unit of the immune response predominance over the effector one. As the decrease of the agranulocytes ratio and the erythrocyte sedimentation rate (ESR) to 55,28 % and the leukocyte ratio index and ESR to 61,54 % indicate intoxication, which is connected with the autoimmune process, and to a lesser extent with the infectious agent which is also confirmed by the lymphocytic granulocytic index decrease to 8,78 %.

Thus, chronic hepatitis C progression is accompanied by the increase of the immunological reactivity of the organism at the expense of the increase of the leukocyte shift index, ratio index of lymphocytes and monocytes, neutrophilic lymphocytic coefficient, index of the ratio of neutrophils and monocytes, as well as of reducing non-specific reactivity. Such changes from the point of nonspecific and specific immune defense (advantage of cellular immune response over humoral protection) create the conditions for the persistence probability in patients` organism with chronic hepatitis C and formation of a chronic process with possible complications in the future (autoimmune processes) [7-10].

CONCLUSIONS

1. General immunological reactivity in patients with chronic hepatitis C increased to 30,07% and the factors activation and mechanisms of nonspecific anti-infection protection decreased that create a condition for prolonged persistence of hepatitis C virus and the progression of a chronic infectious process in patients' organism.
2. The mechanisms of affector unit in the immune response prevail over the effector processes in the immunological reactivity of the patients` organism with chronic hepatitis C which is confirmed by the activation of the microphage system over the acrophage one.
3. The cellular immune response and the reduced humoral link of the immune system (probably due to the infection of B-lymphocytes) prevail in patients with chronic hepatitis C which enables the virus to avoid the humoral control and persist in the organism for some period of time.

REFERENCES

1. Golubovskaya O. Vy`rusnыj gepaty`t – эto dy`agnoz, a ne pry`govor [Viral hepatitis is a diagnosis, not a verdict] Zerkalo nedely`2013 26, 3-4 [in Ukrainian]
2. Speransky`j, Y`.Y`., Samojlenko, G.E., Lobacheva, M.V. Obshhy`j analy`z krovy` – vse ly` ego vozmozhnosty` y`scherpanы? Y`ntegral`nыe y`ndeksы y`ntoksy`kacy`y` kak kry`tery`y` ocenky` tyazhesty` techeny`ya эndogennoj y`ntoksy`kacy`y`, ee oslozhneny`j y` эffekty`vnosty` provody`mogo lecheny`ya. [General blood test - is all his capabilities exhausted? Integral indices of intoxication as criteria for assessing the severity of endogenous intoxication, its complications and the effectiveness of the treatment]. Zdorov`e Ukray`ny,2009 6 (19),3-4, [in Russian].
3. Heim, M., & Thimme, R. Innate and adaptive immune responses in HCV infections. Journal Of Hepatology, 2014 61(1), S14-S25. doi: 10.1016/j.jhep.2014.06.035
4. Ansaldi, F., Orsi, A., Sticchi, L., Bruzzone, B., Icardi, G. Hepatitis C virus in the new era: perspectives in epidemiology, prevention, diagnostics and predictors of response to therapy. World J. Gastroenterol. 2014 20 (29), 9633-9652
5. Lavanchy, D. The global burden of hepatitis C. Liver International, 2009, 29, 74-81. doi: 10.1111/j.1478-3231.2008.01934.x
6. Madaliński, K., Zakrzewska, K., Kołakowska, A. Epidemiology of HCV infection in Central and Eastern Europe. Godzik Przegl Epidemiol,69(3),2015 459-464,581-584.
7. Rezaee-Zavareh, M., Hadi, R., Karimi-Sari, H., Hossein Khosravi, M., Ajudani, R., & Dolatimehr, F. et al. Occult HCV Infection: The Current State of Knowledge. Iranian Red Crescent Medical Journal, 2015 17(11). doi: 10.5812/ircmj.34181
8. Cacoub P., Desbois AC, Comarmond C. & Saadoun D. Влияние устойчивого вирусологического ответа на внепеченочные проявления хронического гепатита С: метаанализ. Gut ,2018, 67 (11), 2025-2034.
9. Руководство AASLD / IDSA HCV, Chung, RT, Davis, GL, Jensen, DM, Masur, H., Saag, MS, & Fontana, RJ. Hepatitis C Guide: AASLD-IDSA Recommendations for Testing, Administering and Treatment of Adults Infected with Hepatitis C Virus. Hepatology, 2015, 62 (3), 932-954.
10. Manns, MP, Buti, M., Gane, E., Pawlotsky, JM, Razavi, H., Terrault, N. & Younossi, Z. Hepatitis Virus C Natural Surveys Primary Diseases, 2018, 3 , 170-176.

The work is performed with in the limits of the department's scientific work. Molecular-genetic and clinical-pathogenetic

features of the combined the pathology of internal organs, the role of infectious, metabolic factors in its development, differentiated approaches to treatment.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Iryna. V. Balaniuk
Higher Educational State Institution Of Ukraine
"Bukovynian State Medical University"
Chernivtsi, Ukraine
tel: +380950740004
e-mail: balanyk85@gmail.com

Received: 04.02.2019
Accepted: 07.06.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

THE STUDY OF ORAL FLUID DYNAMIC PARAMETERS ON THE BACKGROUND OF PATHOLOGICAL AND PHYSIOLOGICAL DENTAL ABRASION

Viktor V. Kovalenko[1], Iryna M. Tkachenko[1], Zoryana Y. Nazarenko[1], Natalia M. Brailko[1], Julia G. Romanova[2], Olga V. Sheshukova[1], Yaroslav V. Vodoriz[1]
UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE
ODESA NATIOANAL MEDICAL UNIVERSITY, ODESA, UKRAINE

ABSTRACT

Introduction: Violation of oral fluid mineralization processes, which is determined by the mineralization potential of saliva, is associated with changes in the physicochemical parameters of the oral fluid, particularly its viscosity.

The aim of our study was to study mineralization potential and types of microstallation of oral fluid as one of the factors of influence on the cariesogenic situation in the oral cavity of patients with physiological or pathological tooth abrasion.

Materials and methods: During the examination of patients' oral cavity, a comprehensive assessment of tooth hard tissues was performed in order to of study activity and prevalence of the processes occurring in them.

Results: Assessing the physico-chemical parameters of oral fluid in patients of the first experimental group, we obtained the following results: the viscosity of saliva in subgroups was 2,17 ± 0,87 for subgroup #1, 1,78 ± 0,57 for subgroup #2, and 2,15 ± 0,86 for #3 subgroups, which did not have a significant difference between the indices within the group. During the research, the number of independent structures of oral fluid in subgroups 1-3 was 1.67 ± 0.86, 1.67 ± 0.77 and 1.57 ± 0.85.

Conclusions: Thus, we have established that the mineralizing function of saliva changes when the cariesogenic situation in the oral cavity arises,. This leads to destabilization of the crystalline structure of the oral fluid and indicates the relationship between its structural and mineralizing properties.

KEY WORDS: abrasion of tooth hard tissues, mineralizing potential of oral fluid, microcrystallization of oral fluid

Wiad Lek 2019, 72, 7, 1315-1319

INTRODUCTION

Saliva is a complex biological fluid that performs tooth mineralization after their erruption and provides the optimal composition during their function [1; 2]. Despite many factors contributing development of dental caries, biological environment of the oral cavity (i.e. oral fluid, which constantly changes its characteristics: quantitative and qualitative composition, mechanisms of protection, etc.) remains the main etiological factor of caries appearance. Violations of the physico-chemical properties of the oral fluid are associated with general and local factors and affect the oral cavity. Thus, those violations contribute to the development of diseases of tooth hard tissues [3].

Recently the understanding of demineralization and remineralization processes of tooth structures, depending on the features of the manifestation of physiological and pathological abrasion and the emergence of carious process, was significantly reconsidered [4]. This concept involves not only treatment of caries using different methods of preparation and bioactive restoration materials, but also early diagnosis of risk factors for the development of caries and their correction. One of the major risk factors is a violation of the oral fluid properties.

An important role in maintaining homeostasis of solid dental tissues belongs to the mineralization function of saliva. The study of the mineralizing properties of the oral fluid by assessing the nature of its microcrystallization in conditions of various external and internal environmental influences remains a relevant research method in terms of diagnosis and prediction of pathological conditions of the organs of the oral cavity.

The composition of the oral fluid plays a major role in the development of a number of the oral cavity diseases, particularly in the development of tooth caries [5]. Violation of oral fluid mineralization processes, which is determined by the mineralization potential of saliva, is associated with changes in the physicochemical parameters of the oral fluid, particularly its viscosity.

THE AIM

The aim of our study was to study the viscosity, mineralization potential and types of microstallation of oral fluid as one of the factors of influence on the cariesogenic situation in the oral cavity of patients with physiological or pathological tooth abrasion.

MATERIALS AND METHODS

During the examination of patients' oral cavity, a comprehensive assessment of tooth hard tissues was performed in order to of study activity and prevalence of the processes occurring in them. The intensity of the carious process was determined according to the DMFT index of teeth (total number of decayed, missing and filled teeth in one surveyed). Evaluation of hygienic condition of oral cavity was performed with a Fedorov-Volodkina's index.

Patients with carious teeth were divided into two groups The first clinical group consisted of 53 patients with chronic advanced caries on the background of physiological abrasion. The second clinical group consisted of 65 patients with chronic advanced caries on the background of pathological abrasion of tooth hard tissues. The classifications of the caries according to its severity and progression have been used. In order to verify the form tooth of abrasion, the classification of Moldovanov (1992) was used [6]. For a more accurate diagnosis the form of abrasion, its prevalence and type of abrasion were also precised.

As filling material we used glass-ionomer cement VITREMER (by 3M). Patients treated with this filling material were assigned to subgroup #1 of the 1st group (21 patients) and to the subgroup #2 of the 2nd group (20 patients). We also used material CHARISMA (by Heraeus Kulzer) as a light curing composite resin material. This material was used in the combination with adhesive systems of 5th generation (Single Bond 2 by 3M) and 7th generation (Adper Easy One by 3M) [7,8] . Depending on the type of adhesive system and the diagnosis of the pathology pathients were assigned to the following subgroups: subgroups #2 of the 1st group (18 patients), subgroups #2 of the 2nd group (23 patients), to subgroups #3 of the 1st group (14 patients), and to subgroups #3 of the 2nd group (22 patients).

The viscosity of the oral fluid was studied according to Redinova`s technique [9]. Mixed saliva was collected in sterile glass test-tubes immediately at the beginning of the study. Then we calibrated 1ml medicine dropper with distilled water with measuring the volume of water that flowed out of it during 5 seconds (Vw.). Having it mounted vertically and filled with 1 ml of saliva we measured the volume of oral fluid that flowed out of the medicine dropper over a period of time (Vs). The viscosity of saliva was determined in relative units according to the formula: $Vs = Vw \cdot Vw / Vs$ (where V w is the volume of water ejected from the dropper (ml); Vs - the volume of saliva that leaked from the dropper (ml); Vw - water viscosity. The average Vs value approaches to 1.46 with significant deviations (1.03-3.74). The Vs value exceding 1.46 is a dangerous prognostic indicator for the emergence and development of carious process.

The mineralization potential of the oral fluid (MPOF) was evaluated by the nature of its microcrystallization (MC) [4]. The principle of this method implies the ability of the crystalline substance to form crystals of various forms and different orientations in all dimensions after drying. A portion (0.2-0.3 ml) of mixed saliva was taken from the flor of the oral cavity with a sterile pipette. At least 3 drops of saliva were applied on a slide glass, pre-treated with alcohol. Drying procedure was carried out at room temperature. The dried glass were packed in containers and sent to the laboratory for research. The structure of crystallograms was evaluated macroscopically (quantity of crystallization centers and the character of the image) and microscopically (structure and changes of crystals).

The structure of saliva samples was studied with an optical microscope «Leica DLMS-LS» (Germany) and camera «Nikon DM v.581-80. Primary scanning of entire surface of the drop was performed under the small magnification. Secondary scanning of certain areas with different morphology was performed under the large magnification. Selected areas of crystallographs were photographed and saved.

Determination of microcrystallization types was performed according to the following types of MC. Also, whole surfaces of drops were reexamined in order to determine the mineralization potential of the oral fluid (MPOF). The formula: $MPOF = \Sigma MC / 3$ (where MPOL - mineralization potential of oral fluid, recorded in points, Σ MC - sum of microcrystallization types of oral fluid).

Microcristalisation evaluation was carried out according following schema: I type was characterized by a clear pattern of large elongated crystallographic structures, merged together and had a tree or fern-shaped form, located mainly in the center of the drop. Organic part was placed along the periphery in a small amount. This type of microcrystallization received 5 points; II type had a separate dendritic crystalloplasty structure in the center of the drop, smaller comparing to the I type. A large number of crystalline structures of irregular shape were placed on the periphery. This type received 3 points; III type had crystals of different shapes, which were placed evenly in the form of a mesh in the field of . A lot of organic part was still in the field of view. III type received 2 points; Type IV had a large number of isometrically placed irregular structures throughout the drop surface; 1 point. V type did not recieved any points due to the absence of crystals in the field of view.

Analysis was performed regarding to the total area of the drop of saliva [4], expressing in ponts the crystallization level: 1 point - very low, 2 points - low, 3 points - satisfactory, 4 points - high, 5 points - very high, which corresponded I, II, III types by. Leus and Dubrovna [6].

All work was conducted in accordance with the Declaration of Helsinki (1964) and was approved by the Ethical Committee of the academy.

RESULTS AND DISCUSSION

Assessing the physico-chemical parameters of oral fluid in patients of the first experimental group, we obtained the following results: the viscosity of saliva in subgroups was $2,17 \pm 0,87$ for subgroup #1, $1,78 \pm 0,57$ for subgroup #2, and $2,15 \pm 0,86$ for #3 subgroups, which did not have a significant difference between the indices within the group. During the research, the number of independent structures of oral fluid in subgroups 1-3 was 1.67 ± 0.86, 1.67 ± 0.77 and 1.57 ± 0.85. Depending on the characteristics of independent struc-

Table I. Viscosity and degree of oral fluid mineralization of patients from the experimental groups (M ± m).

Parameters	Groups	Quantity of patients	Results recieved	Possible fault
Saliva viscosity (μ)	I	53	1,95 ± 0,73	≤ 0,05
	II	65	2,25 ± 0,91*	
Quantity of independent structures	I	53	1,64 ± 0,81	≤ 0,05
	II	65	2,4 ± 0,58*	
Mineralizing potential of oral fluid	I	53	2,37 ± 1,42	≥ 0,05
	II	65	2,58 ±0,69	
I type of microcristalization	I	53	0,54±0,74	≥ 0,05
	II	65	0,84±0,59	
II type of microcristalization	I	53	0,64 ± 0,48	≥ 0,05
	II	65	0,64 ± 0,62	
III type of microcristalization	I	53	0,67 ± 0,47	≤ 0,05
	II	65	1,13 ± 0,56*	
IV type of microcristalization	I	53	0,82 ± 0,51	≥ 0,05
	II	65	0,41 ± 0,49	
V type of microcristalization	I	53	0	≤ 0,05
	II	65	0,046 ± 0,21*	

Notes: * - the reliability of the difference between the values of p≤0,05

Table II. DMFT and hygienic indices results.

Indices	Subgroups	Quantity of patients	Results, M ±m
DMFT	1	21	14,38±4,74
	2	18	12,06±3,78
	3	14	12,79±4,02
Hygienic index	1	21	1,91±0,20
	2	18	1,82±0,17
	3	14	1,84±0,18

tures, the mineralizing potential of oral fluid for subgroup 1 was 2.38 ± 1.42, for the subgroup 2 - 2.23 ± 1.47 and for the subgroup 3 - 2.38 ± 1.42, which is a satisfactory prognostic sign for the emergence of a carious process (Table I).

When comparing the viscosity of saliva, we noticed a significant difference in the rates among patients in groups I and II. The mineralizing potential of the oral fluid also has a significant difference in the groups.

The hygienic state of the oral cavity according to the Fedorov-Volodkina`s index was mostly determined as satisfactory or unsatisfactory. The condition of hygiene of the oral cavity, assessed as a good one, was seldom. Patients who were already divided into groups had practically the same level of oral hygiene 1.86 ± 0.189 for patients in group I and 1.83 ± 0.13 for patients in group II with p ≥ 0.05. (Table II).

The mineralization potential of the oral fluid also had a significant difference in the studied groups:

WE should also note that:

- viscosity of saliva has a correlation with DMFT index in groups (p = 0.001);
- DMFT and hygienic indices are influenced by the type of microcrystallization. The III type has a correlation with the DMFT index (p = 0.005), GI (p = 0.007) and with viscosity (p = 0.001) and the number of independent structures (p = 0.001);
- IV type of microcrystallization has a strong correlation with viscosity (p = 0.007), the number of independent structures (p = 0.0078) and with mineralizing potential of the oral fluid (p = 0.0001). A connection was also established between structures of IV type and I and II type of crystallization;
- The V type of microcrystallization of the oral fluid correlates with the values and indices of type II and III (p = 0.0009 and p = 0.0008 respectively).

Therefore, I and II types of microcrystallization are predominant in caries resistant patients, type III is more typical for patients with a tendency to formation of carious cavities. Even in the case of pathological tooth abrasion in patients of the II experimental group, the III type of microcrystallization was more prevalent.

Mineralizing potential of oral liquid in patients from experimental groups depends on the number of independent structures in the patients of the I group (2.37 ± 1.42) and 2.58 ± 0.69 in patients of the II group (p ≤ 0.05) .

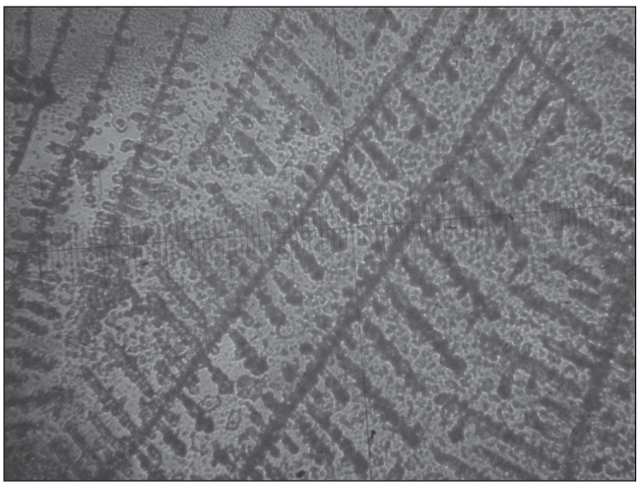


Fig. 1. Microphotography of an independent structure and I type of of the patient from II group with DMFT = 3. Patient V., 32 years.

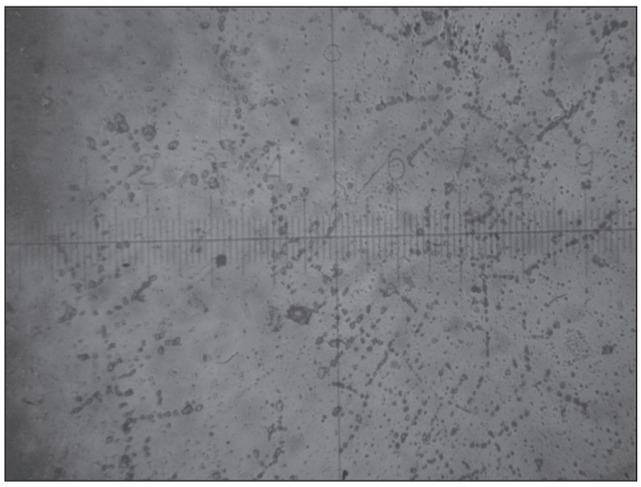


Fig. 2. Microphotography of the oral fluid structure of the patient N., 40 years of age, group I, subgroup 3 with I-II microcrystallization type structures (in the center of the experimental site).

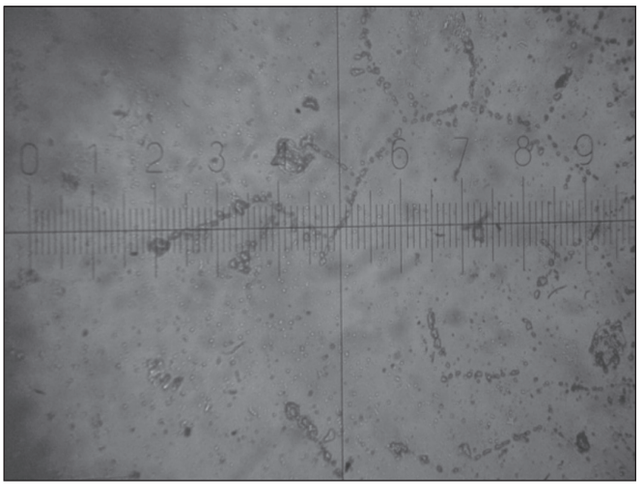


Fig. 3. Microphotography of the oral fluid structure of the patient N., 40 years of age, group I, subgroup 3 with I-II microcrystallization type structures (on the periphery).

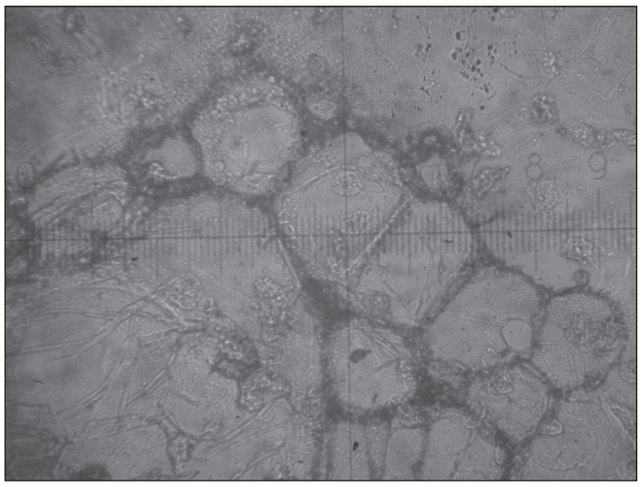


Fig. 4. Microphotography of an independent structure of the third group of dried oral liquids of the patient of group II. Patient V., 26 years old. Independent structure III with "cellular" structures are visible.

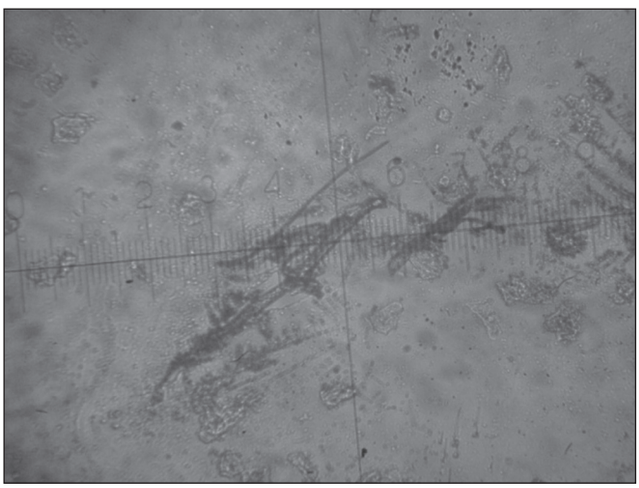


Fig. 5. Microphotography of an independent structure of the third group of dried oral liquids of the patient of group II. Patient V., 26 years old. Independent structure III with "filamentary" structures are visible.

Type I of microcrystallization was typical for patients with low DMFT I and II group (Fig.1).

Type II of microcrystallization was characterized by separate dendritic crystalloplasty structures in the center of the drop, smaller comparing to the first type. A large number of crystalline structures of irregular shape were located along the periphery. In the study, we have the opportunity to note the different density of crystalline structures throughout the surface of the sample (Fig.2-3).

III type had crystals of different shapes, which were placed evenly in the form of a mesh across all the field of vision. A lot of organic part was also present. In this type of microcrystallization, a strong correlation between DMFT, hygienic indices and type of microcrystallization was also detected (Fig.4-5).

All characteristics are interrelated and exist in one complex. Changes of one parameter may result in other changes of another. Therefore, it was quite interesting

to study oral fluid microcrystallization in patients of the above-mentioned groups and to establish differences between the presence of different structures in these patients.

Thus, a significant difference in the presence of structures I, II, II , V and the mixed structure I + II in patients of II group ($p < 0,05$). Also, a differenc in mass fractions in oral fluid samples of structures I, II, III, and V was revelaed. During the study of microcrystallization data of patients of I Group the prevalence of type III structures and mixed structures of type I + II was determined.

Comparing data of groups I and II we found a difference in the values of the indicators of structure I and the mixed structures I + II, I + II + III, I + II + IV and also I + II + V, which may lead to the influence of various factors on the ratio and formation of mixed structures, as well as the peculiarity of processes occurring in the oral liquid for the manifestation of the carious process in the physiological and pathological tooth abrasion.

CONCLUSIONS

Thus, we have established that the mineralizing function of saliva changes when the cariesogenic situation in the oral cavity arises,. This leads to destabilization of the crystalline structure of the oral fluid and indicates the relationship between its structural and mineralizing properties. In this aspect, we recommend an integral assessment of the morphology of tooth hard tissues and oral fluid in order to choose the restorative material and the features of defect of tooth hard tissues restoring in the case of physiological and pathological abrasion.

REFERENCES

1. Korotkih N.G., Pashkov A.N., Bolgov S.V., Loshkarev V.P. Vliyaniye faktorov vneshney sredy na kristallizatsiyu rotovoy zhidkosti. [The influence of environmental factors on the crystallization of oral fluid]. Stomatology. 2002; 4. 13-16. (Ru)
2. Mitropanova M.N., Znejbat M.S., Pavlovskaya O.A. etal. Vliyanie bufernoj sistemy na remineralizaciyu tverdyh tkanej zuba [Effect of the buffer system on the remineralization of tooth hard tissues] J Problems of stomatology.2013; 2:69-75. (Ru)
3. Tkachenko I.M., Brailko N. N., Kovalenko V. V. [et al.] Morfologicheskoye issledovaniye emali i dentina zubov s karioznym protsessom i nekarioznymi porazheniyami. [Morphological study of tooth enamel and dentin with carious process and non-carious lesions]. Wiadomości Lekarskie. 2018; 71 (5). 1001–1005. (Ru)
4. Tkachenko I. M. Vyznachennya shchil'nosti emali zubiv, yak kryteriyu vynyknennya pidvyshchenoyi stertosti zubiv. [Determination of tooth enamel density as a criterion of increased tooth abrasion appearance] World of Medicine and biology. 2012; 2. 166-170. (Ru)
5. Pavlenkova E.V., Tkachenko I.M., Tkachenko A.I., Pavlenko S.A. Zavisimost krayevoy adaptatsii kompozitnykh plomb v polostyakh II klassa po Bleku ot sostoyaniya gigiyeny polosti rta i intensivnosti kariyesa [Dependence of the edge adaptation of composite fillings in cavities II class on the state of oral hygiene and intensity caries]. Wiadomości Lekarskie. 2017. 70 (3). 574-577. (Ru)
6. Moldovanov, A.G. Etiologiya, vozrastnyye aspekty patogeneza, kliniki, diagnostiki, lecheniya i profilaktiki povyshennogo istiraniya tverdykh tkaney zubov/ [Etiology, age-related aspects of pathogenesis, clinical picture, diagnosis, treatment and prevention of increased abrasion of hard dental tissues] MD thesis. 1997; p. 36. (Ru)
7. Tkachenko IM, Kovalenko VV, Skrypnikov PM. [et al.]. Reasoning of adhesive system choice for treatment of patients with increased tooth wear. Wiadomosci Lekarskie. 2018; 71 (6).1129–1134.
8. Vodoriz, YY. Marchenko IY, Shundryk MA. [et al.] Review of treatment methods of patients with uncomplicated teeth fractures. Wiadomosci Lekarskie. 2018. 71 (7). 1360–1364.
9. Redinova T. L., Pozdeev A. R. Klinicheskiye metody issledovaniya slyuny pri kariyese zubov: Metod. rekomendatsii dlya subordinatorov, internov i vrachey-stomatologov. [Clinical methods for the study of saliva in dental caries] Izhevsk. 1994; p.24. (Ru)

This investigation is a fragment of the research of the Ukrainian stomatological academy "Morpho functional characteristics of oral cavity tissues and their impact on therapeutic measures and the choice of treatment materials. Registration number 01145U001112. No external funding was received during for this investigation. There is no conflict of interests between authors and other organizations.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Yaroslav Y. Vodoriz
17 Zalizna Street, 36001 Poltava, Ukraine
tel:+380505420497
e-mail: yaroslavvodorez@gmail.com

Received: 25.02.2019
Accepted: 29.05.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

OPTIMIZATION OF THE TREATMENT OF ROTAVIRUS INFECTION IN CHILDREN BY USING *BACILLUS CLAUSII*

Oleksandr I. Smiyan[1], Kateryna O. Smiian-Horbunova[1], Tetiana P. Bynda[1], Andrij M. Loboda[1], Sergij V. Popov[1], Ihor Yu. Vysotsky[1], Oleksandr P. Moshchych[2], Olena G. Vasylieva[1], Yuliia A. Manko[1], Olena L. Ovsianko[1], Mariia V. Kolesnikova[1], Natalia O. Dolgova[1], Tatiana O. Aleksakhina[1], Bara' Al-Rawashdeh[1]

[1] SUMY STATE UNIVERSITY, SUMY, UKRAINE

[2] NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KIEV, UKRAINE

ABSTRACT

Introduction: Rotavirus infection is a leading place in the structure of acute intestinal infections in children. Rotavirus is excreted in 40–60 % of children hospitalized with gastroenteritis all over the world. Every year, 2 million patients are hospitalized with a severe form of RVI, 25 million need medical help from a doctor and 111 million cases are treated at home.

The aim: The purpose of our study was to optimize the treatment of rotavirus infection in children by using *Bacillus clausii*.

Materials and methods: There were 65 children with a rotavirus infection under supervision. The control group was consisted of 28 practically healthy children. The study of humoral immunity was carried out on the basis of determining the serum content of immunoglobulin G, immunoglobulin M, immunoglobulin A, and secretory immunoglobulin A in coprofiltrate. In the process of treatment, the children were divided into two groups: the first received standard treatment, the second group were added to standard treatment with a probiotic drug (*Bacillus clausii*).

Results: In children with RVI with modified treatment main symptoms were reduced compared with the children receiving standard treatment, ($p < 0.001$). In patients with rotavirus infection in the acute period of the disease, a decrease in the concentration of IgA ($p < 0.001$) and an increase in IgM ($p < 0.001$) in serum and a decrease in sIgA ($p < 0.001$) in coprofiltrate was observed in comparison with children in control group. In the period of reconvalescence in children after the traditional treatment, it wasn`t revealed normalization of the immunoglobulins. Patients receiving a probiotic drug in addition to traditional treatment it was revealed normalization of the parameters of serum immunoglobulins A, M, G and sIgA in coprofiltrate.

Conclusions: So, the probiotic drug containing *Bacillus clausii* has a positive effect on the humoral immune system in children with rotavirus infection.

KEY WORDS: rotavirus, humoral immunity, children, IgA, sIgA, IgM, IgG

Wiad Lek 2019, 72, 7, 1320-1323

INTRODUCTION

Rotavirus infection (RVI) is an urgent problem, because it is extremely widespread, especially among young children, is characterized by the severity of the course and the frequency of adverse outcomes and consequences [1]. Rotavirus infection is a leading place in the structure of acute intestinal infections in children [2]. Rotavirus is excreted in 40–60 % of children hospitalized with gastroenteritis all over the world. Every year, 2 million patients are hospitalized with a severe form of RVI, 25 million need medical help from a doctor and 111 million cases are treated at home [3, 4]. The most severe illness occurs in children at the age of 4-36 months life. Annually, rotavirus infection causes more than 600,000 deaths in children under the age of 5 who die from severe dehydration and electrolyte imbalance [5, 6]. Almost every young child is infected with rotavirus regardless of place of residence and socio-economic status [7].

Infection of the intestine with rotavirus depends on many factors: such as pH of the gastric juice, the presence of trypsin in the secretion of the duodenum, the level of secretory IgA and the features of the morphology of the mucous membrane. The virus is tropical to the cells of the cylindrical epithelium, located on the villi of the duodenum and in the upper parts of the small intestine [8]. Protection of the human body from the rotavirus is ensured by the components of cellular and humoral immunity [9]. Antibodies protect not only from the development of clinical manifestations of RVI, but also from infection. This protection depends on the level of antibodies: high-titers children are completely protected from rotavirus infection [10, 11]. These facts determine the need for effective therapeutic and prophylactic measures against rotavirus gastroenteritis.

THE AIM

The purpose of our study was to optimize the treatment of rotavirus infection in children by using *Bacillus clausii*.

MATERIALS AND METHODS

Under observation, there were 65 children with RVI from 6 months to 5 years old (main group) who were treated at

the Communal Nonprofit Enterprise "Children's Clinical Hospital of St. Zinaida" of Sumy City Council.

All children were enrolled in the study after informed consent from their parents or guardians. Ethical approval was obtained from Institutional research ethics committees.

Criteria for inclusion:

- age from 6 months to 5 years;
- rotavirus infection;
- hospitalization in acute phase of the disease;
- informed consent from children's parents or guardians;
- the absence of comorbidity in patients;
- children didn't take drugs, which were contributed to the change in the amount of trace elements.

Criteria for exclusion:

- age less than 6 months, or more than 5 years;
- Acute intestinal infection of another viral or bacterial etiology, as well as mixed variants of rotavirus infection (with other viruses or bacteria).
- hospitalization in mild phase of the disease;
- parents or guardians of children didn't give informed consent;
- presence of comorbidity in children.

Diagnosis of acute intestinal infection of rotavirus etiology was verified according to anamnesis, parent complaints, subjective and objective symptoms, and the results of the immuno-chromatographic test «CITO TEST ROTA» by Pharmaco Ltd. The control group consisted of 28 practically healthy children. The study was conducted during the acute period of the disease (for 1-2 days) and during the reconvalescence period (5-6 days). During the study, the children of the main group were divided into two groups: the I group consisted of 34 children with RVI who received standard treatment (symptomatic therapy, sorbents, rehydration therapy), and the second group included 31 children with RVI who had received standard treatment A probiotic drug containing spores of the polysaccharide strain *Bacillus clausii* - 2 × 109 and purified water (1 vial 1 time per day) is added. The study of humoral immunity was based on the determination of the content of immunoglobulin G (Ig G), immunoglobulin M (Ig M) and immunoglobulin A (Ig A) by the method of radial immunodiffusion in agar for Mancini G [12]. The level of secretory immunoglobulin A (sIg A) was determined in the excrements by the immune enzyme with the method using the «Vector Best» test systems (Novosibirsk, Russia). Statistical processing of the data was carried out by generally accepted methods of variation statistics. The following indicators were determined: arithmetic average (M), average error (m), level of differences between the two mean values (confidence probability - p). Calculations were made on a personal computer using Microsoft Excel programs adapted for medical and biological research.

RESULTS AND DISCUSSION

The main clinical symptoms in children with rotavirus infection were: hyperthermia, vomiting and diarrhea. At an objective examination of children with RVI patients, reduced elasticity of the skin and turgor of soft tissues was revealed, which is a manifestation of exclusion due to the general dehydration of the organism. Children with RVI with deep palpation of the abdomen noted pain in the epigastrium and umbilical region, as well as rumbling along the intestinal tract. Moreover, clinical signs I and II had no significant differences ($p > 0,05$). In children with RVI with modified treatment, signs of general weakness disappeared by 1.17 days ($p < 0.001$) earlier than in children receiving standard therapy. For patients in this group, the duration of treatment was characterized by a reduction in the duration of swelling and / or abdominal pain by 0.72 days ($p < 0.05$) compared with standard treatment children. In patients with modified treatment, the raised body temperature was shorter by 0.52 days, compared with standard treatment ($p < 0.05$). In addition, patients in group II reduced the duration of diarrhea by 1.13 days ($p < 0.001$), and shortened vomiting by 0.6 days ($p < 0.001$) compared with children in group I. Along with this, there was no significant difference between the I and II groups regarding the duration of clinical symptoms such as pallor of the skin and appetite disturbance ($p > 0.05$).

In the period of the onset of the disease in patients with rotavirus infection (the main group) it was observed a significant reduction of IgA levels (0.58 ± 0.02) g / l compared to the similar indicator of children in the control group (0.82 ± 0.02) g / l ($p < 0.001$) (Table I). While the concentration of IgM was (1.01 ± 0.02) g / l and was significantly higher than the similar indicator of the control group (0.73 ± 0.02) g / l ($p < 0.001$), and the IgG level (8,42 ± 0.18) g / l did not differ significantly from the children in the control group (7.96 ± 0.21) g / l ($p > 0.05$). The secretory IgA in coprofiltrate in patients with CVI decreased to (23.15 ± 0.42) mg / l in relation to the data of virtually healthy children (31.18 ± 0.63) mg / l ($p < 0.001$).

The period of reconvalescence in children of group I after the traditional treatment was characterized by an increase in IgA to (0.71 ± 0.02) g / l ($p < 0.001$) and IgG (9.32 ± 0.19) g / l ($p < 0, 05$). While the concentration of IgM before discharge from the hospital decreased and it was (1,03 ± 0,03) g / l ($p > 0,05$). The level of secretory IgA in coprofiltrate in sick children increased and amounted to (27.10 ± 0.31) mg / l ($p < 0.001$).

Patients in the 2nd group, who received a probiotic drug in addition to traditional treatment, showed normalization of serum immunoglobulin A, M, G, and secretory immunoglobulin A in coprofiltrate.

The results of many studies indicate a positive effect of probiotic drugs on the course of acute and persistent diarrhea [13, 14]. In the study, researchers point to a decrease in the duration of diarrhea in children with acute intestinal infections, which was additionally designated *Bacillus clausii* [15]. Currently, the most well documented probiotic bacteria used in human therapy are lactic acid bacteria. In contrast, studies aimed at studying the mechanisms responsible for the probiotic positive effects of Bacillus are rare.

Table I. Dynamics of indicators of humoral immunity in children suffering from rotavirus infection, depending on the performed therapy, M ± m

Immunological index	Control group (n=28)	Main group		
		before treatment (n=65)	after treatment (n=65)	
			I group (n=34)	II group (n=31)
	1	2	3	4
Ig A, g / l	0,82 ± 0,02	0,58 ± 0,02 $p_{1-2} < 0,001$	0,71 ± 0,02 $p_{1-3} < 0,001$ $p_{2-3} < 0,001$	0,86 ± 0,03 $p_{1-4} > 0,05$ $p_{2-4} < 0,001$ $p_{3-4} < 0,001$
Ig G, g / l	7,96 ± 0,21	8,42 ± 0,18 $p_{1-2} > 0,05$	9,32 ± 0,19 $p_{1-3} < 0,001$ $p_{2-3} < 0,05$	9,11 ± 0,22 $p_{1-4} > 0,05$ $p_{2-4} > 0,05$ $p_{3-4} > 0,05$
Ig M, g / l	0,73 ± 0,02	1,01 ± 0,02 $p_{1-2} < 0,001$	1,03 ± 0,03 $p_{1-3} < 0,001$ $p_{2-3} > 0,05$	0,79 ± 0,03 $p_{1-4} > 0,05$ $p_{2-4} < 0,001$ $p_{3-4} < 0,001$
sIg A, mg / l	31,18 ± 0,63	23,15 ± 0,42 $p_{1-2} < 0,001$	27,10 ± 0,31 $p_{1-3} < 0,001$ $p_{2-3} < 0,001$	30,32 ± 0,39 $p_{1-4} > 0,05$ $p_{2-4} < 0,001$ $p_{3-4} < 0,001$

Notes: p_{1-2}-the reliability of the difference between the indicators of the primary group's children before treatment and the control group; p_{1-3} – the reliability of the difference between the indicators of children in group I after treatment and control group; p_{2-3} - the reliability of the difference between the indicators of the children of the main group before treatment and Group I after treatment; p_{1-4} - the reliability of the difference between the indicators of children of group II after treatment and the control group; p_{2-4} - the reliability of the difference between the indicators of the children of the main group before treatment and the second group after treatment; p_{3-4} - the reliability of the difference between the indices of children of the 1st and 2nd groups after treatment.

In the work of Urdaci, M. C., Bressollier, Ph., Pinchuk, I. (2004) evaluation of the immunomodulating properties of probiotic strains of B. clausii was performed in vitro on Swiss and C57 Bl / 6j mouse cells. The authors demonstrate that these strains in their vegetative forms are able to induce the activity of NOS II synthetase, IFN-γ production and the proliferation of CD4 + T cells [16].

The results of our study showed a decrease in the concentration of class A immunoglobulin and an increase in IgM in children with rotavirus infection, which may indicate the activation of the antibody formation in the acute period of the disease, against the background of an increased local response to antigenic stimulation in the intestine. Decreased IgA concentrations may be due to immaturity of the immune function of the intestine in young children and / or poor adhesion of the virus and neutralizing ability. At the same time, a slow "immunological start" or transient hypogammonoglobulinemia in young children may explain insufficient IgG and IgA levels during the infectious process. During the treatment of children with rotavirus diarrhea in the acute period of the probiotic preparation containing *Bacillus*, there was a rapid positive dynamics of the course of the inflammatory process: the immunological parameters reached the level of children in the control group.

So, the probiotic drug containing *Bacillus clausii* has a positive effect on the humoral immune system in children with rotavirus infection.

According to the results of our study, it was found that in children with rotavirus infection a decrease in the level of immunoglobulin of class A and an increase in IgM was observed. A low level of IgA during the infectious process may be due to immaturity of the immune function of the intestine in children or a slow "immunological start" in and / or poor adhesion of the virus and neutralizing ability. An increase in Ig M may indicate activation of the antibody formation in the acute period of the disease, against the backdrop of an increased local response to antigenic stimulation in the intestine. When included in the treatment of children with rotavirus diarrhea in the acute period of the probiotic preparation containing *Bacillus clausii*, there was a rapid positive dynamics of the course of the inflammatory process: reduction of clinical symptoms and normalization of immunological parameters.

Thus, the use in the complex treatment of rotavirus infection of a probiotic drug containing *Bacillus clausii*, contributed to improving the effectiveness of treatment.

CONCLUSIONS

1. The inclusion of *Bacillus clausii* in the treatment of children with rotavirus infection contributed the reduction in the duration of clinical symptoms.
2. In children with rotavirus infection in the acute period of the disease, there was a decrease in the concentration

of IgA and an increase in the level of IgM in serum and a decrease in sIgA in coprofiltrate.

3. During the period of reconvalescence in children with rotavirus infection after standard treatment, the humoral link of the immune system was characterized by improvement of the indicators, however, they did not reach the level of control group children.
4. In patients with rotavirus infection, which had been added to the traditional treatment with *Bacillus clausii*, the indices of the humoral immune system reached the level of control group children.

Prospects for further research: It will be perspective to further studying the effects of this probiotic drug on other parts of the immune system of children.

REFERENCES

1. Sai L, Sun J, Shao L et al. Epidemiology and clinical features of rotavirus and norovirus infection among children in Ji'nan, China. Virology journal. 2013; 10(1): 1. DOI: 10.1128 / JCM.02927-13.
2. John BM, Devgan A, Mitra B. Prevalence of rotavirus infection in children below two years presenting with diarrhea. Medical journal armed forces India. 2014; 70(2): 116–119. https://doi.org/10.1016/j.mjafi.2014.02.008.
3. Moradi-Lakeh M, Shakerian S, Yaghoubi M et al. Rotavirus infection in children with acute gast.roenteritis in Iran: A systematic review and meta-analysis. International journal of preventive medicine. 2014; 5(10): 1213–1223.
4. Van Trang N, ThiBich VuH, ThiHong LeN et al. Association between norovirus and rotavirus infection and histo-blood group antigen types in Vietnamese children. Journal of clinical microbiology. 2014; 52(5): 1366–1374. doi: 10.1128/JCM.02927-13.
5. Troeger C, Khalil IA, Rao PC et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. JAMA pediatrics. 2018; 172(10): 958-965. doi: 10.1001/jamapediatrics.2018.1960.
6. Simwaka JC, Mpabalwani EM, Seheri M et al. Diversity of rotavirus strains circulating in children under five years of age who presented with acute gastroenteritis before and after rotavirus vaccine introduction, University Teaching Hospital, Lusaka, Zambia, 2008–2015. Vaccine. 2018; 36(47): 7243-7247. https://doi.org/10.1016/j.vaccine.2018.03.035.
7. Mchaile DN, Philemon RN, Kabika S et al. Prevalence and genotypes of Rotavirus among children under 5 years presenting with diarrhoea in Moshi, Tanzania: a hospital based cross sectional study. BMC research notes. 2017; 10(1): 542. doi: 10.1186/s13104-017-2883-3.
8. Saxena K, Blutt SE, Ettayebi K et al. Human intestinal enteroids: a new model to study human rotavirus infection, host restriction and pathophysiology. Journal of virology. 2015; 90(1): 43-56. doi: 10.1128/JVI.01930-15.
9. Mazankova LN, Gorbunov SG, Shishkina AA. Features of the course and prevention of rotavirus infection in children of early age: studying. Method manual; HBOU DPO "Russian Medical Academy of Postgraduate Education". 2015.
10. Maffey L, Vega CG, Miño, S et al. Anti-VP6 VHH: an experimental treatment for rotavirus A-associated disease. PloS one. (2016); 11(9): e0162351. https://doi.org/10.1371/journal.pone.0162351.
11. Walker LM, Burton DR. Passive immunotherapy of viral infections:'super-antibodies' enter the fray. Nature Reviews Immunology. (2018); 18(5): 297. https://doi.org/10.1038/nri.2017.148
12. Mancini G, Carbonare A, Harmans J. Immunochemical quantitation of antigens by single radial diffusion. Immunochemistry. 1965; 2: 235–239.
13. Sharif MR, Kashani HH, Ardakani AT et al. The effect of a yeast probiotic on acute diarrhea in children. Probiotics and antimicrobial proteins. 2016; 8(4): 211-214. https://doi.org/10.1007/s12602-016-9221-2
14. Liévin-Le Moal, Servin AL. Anti-infective activities of lactobacillus strains in the human intestinal microbiota: from probiotics to gastrointestinal anti-infectious biotherapeutic agents. Clinical microbiology reviews. 2014; 27(2): 167-199. DOI: 10.1128/CMR.00080-13
15. Akter S, Aziz MA, Sharmin KN et al. Anti-Diarrhoeal Effects of Probiotics on Children. Research & Reviews: A Journal of Microbiology and Virology. 2018; 8(1): 15-21.
16. Urdaci MC, Bressollier Ph, Pinchuk I. *Bacillus clausii* Probiotic Strains: Antimicrobial and Immunomodulatory Activities. Journal of Clinical Gastroenterology. 2004; 38: 86-90 doi: 10.1097/01.mcg.0000128925.06662.69.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Oleksandr I. Smiyan
Department of Pediatrics,
Sumy State University,
28 Troytska Str., 40022 Sumy, Ukraine
tel: +380506316005
e-mail: smiyana@ukr.net

Received: 17.02.2019
Accepted: 18.06.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

AREAS FOR FURTHER IMPROVEMENT OF LEGISLATIVE REGULATION OF PATIENTS' RIGHTS IN UKRAINE

Tetyana B. Vilchyk, Alla K. Sokolova
YAROSLAV MUDRYI NATIONAL LAW UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

Introduction: The article reviews issues of legal regulation of patients' rights in Ukraine, analyzes the patient-doctor relationship, proposes the legislative approval of new patients' rights and the need of adoption of a single legislation of these rights.

The aim of this work is to conduct a detailed study of legal regulation of patients' rights in Ukraine and the EU countries, to identify the areas for further improvement of the legislative regulation of patients 'rights in Ukraine, ways of harmonization of national legislation with international standards, which regulate patients' rights.

Materials and methods: we analyzed national and international regulation of patients' rights, case law of the European Court of Human Rights (ECHR), national court judgments. We also used historical, comparative-legal methods, and instruments of analytical research and empirical study.

Conclusions: In Ukrainian law many patient rights are not defined, but are applied in medical practice, therefore, they require legal regulation. In particular, they include: the right to convene a consilium; the right to refuse medical interference; the right to terminate treatment, etc. In addition, with the development of medicine, scientific and technological progress, there are some issues, which arise and need to be legally defined, among them: the rights and responsibilities of the patient during transplantation, artificial insemination, medical research, etc. When making health policy, the concept of trust and respect for patients, their autonomy or constructive partnership with them should be taken into account. Doctors need to take a more active part in discussions and debates with patients. Independence of patients in decision making processes must be provided by law, and the rights and obligations of all parties must be clearly reflected in the relevant documents.

KEY WORDS: patients' rights, legal status of patient, liability for the violation of the patient right, doctor–patient relationship, medical error

Wiad Lek 2019, 72, 7, 1324-1329

INTRODUCTION

Patients' rights are occupying a prominent place in health care, because the patient is the focus of attention in this field, is a key figure in medical-legal relations, to which, to varying degrees, bound all other entities participating in the organization, provision or direct of medical assistance.

Violation of patients' rights is a socially harmful act, impunity of which also affects social security. Domestic law provides a whole range of patients' rights, however, on the one hand, there can be some serious problems with their enforcement, and on the other - in globalization era the new patient rights need to be legally defined. The patients' rights require state guarantees through the formation of an effective public health policy, the establishment of an effective mechanism for their implementation, protection and legal provision. International human rights standards forms the starting point for the development of national health strategies, including in the field of patient rights protection. The EU countries have a wealth of experience in regulating of patients' rights. The patients' rights in EU countries are considered as an important component of the individual level of legal protection and their regulation is a standard for most developed countries, Ukraine must follow this standards too. It is proved that the formation of the domestic legal and regulatory framework for the patient rights should be based on a single concept, the starting point of which is defined: taking into account the provisions of international standards in the field of patient rights; observance of the patient rights; ensuring mutual respect and mutual responsibility in the relationships between the doctor and the patient; the implementation of moral and ethical principles in the legal regulation of healthcare; patient-centered approach to the provision of healthcare.

THE AIM

The aim of this work is to identify the areas for further improvement of the legislative regulation of patients 'rights in Ukraine, harmonization of national legislation with international legal acts on patients' rights.

MATERIALS AND METHODS

We analyzed national and international regulations for patients' rights, case law of the European Court of Human Rights (ECHR), national court judgments. We were used historical, comparative-legal methods, and instruments of analytical research and empirical study.

REVIEW AND DISCUSSION

The history of mankind is the history of struggling for human rights and freedoms. It is the state of human rights and

freedoms that is the determining indicator of humanity, civilization, the culture of any society and its state. Health is a prerequisite for the existence and proper living of any person and any nation. An unhealthy nation has no chances for development and progress. Health care in Ukraine today largely does not correspond to the principles that characterize it as a system. Some parts of the system are not interlinked ideologically and practically operate on the basis of fulfillment of their own goal - profit, while the specificity of the health care system in a social state, which declared itself Ukraine, is that its main goal is to provide for all segments of the population equal opportunity to increase the duration and improve the quality of life.

Scientists have pointed out that the patient rights as a phenomenon, term and legal structure are derivatives of human rights to the extent that the patient is a person. The patient is the main and special subject in healthcare, who wants to get effective health care from medical professionals, and the latter are obliged to provide such assistance [1; 2]. The patient's phenomenon is fundamental to modern law and medical ethics. The patient rights are inherent only to those who have the appropriate special legal status. According to A. Pishita, the legal status of a patient is the system of rights, freedoms, legal guarantees of their implementation and protection, as well as the duties of the person who is the subject of medical-legal relations, enshrined by the state in the legislative procedure [3, p. 95]. L.Samilyk said: "The patient rights as one of the elements of its legal status are the legal rights of a person and are derived from legally established rules" [4]. The legal status of the patient is a changeable legal phenomenon.

A group of authors role of the patient makes sense only in conjunction with doctors who are the main people responsible for health improvement with a certain system of expectations and behavior on the basis of bilateral rights, responsibilities and relationships [5, p.86]. The phenomenon of understanding the role of the bill was proposed by the American sociologist Talcott Parsons. He argued: "The doctor's control over the patient health state is dominant, because it is the doctor who legitimizes the role of the patient, and this is a system of paternalistic relations, which is directed at the doctor, the patient to a certain moment is passive" [6]. According to S.Dutchak, the relationship in the doctor-patient system are historically based on the patient's trust in the doctor. This position is due to the mythological basis of the world, as well as the doctrine in the Christian world. Historically, the first experience of normative prediction of the legal responsibility of a doctor for harm to a patient appears in the King Hammurabi's Laws (Ancient Babylon). The punishment of a doctor for violating the rights of "equal" patients in case of grave consequences was aimed at securing other patients by depriving the doctor of the possibility to continue his medical practice (Babylon, Ancient Egypt and Greece) [7].

The key aspects of the system of relationship between the doctor and the patient is the medical-preventive process, the agreement conditions of its participants in the provision of medical services. The patient cannot independently assess his/her health and take care of recovery [6] due to the lack of significant amount of specialized information, experience and own lack of professionalism in the field of medicine.

During the 72 session of the World Health Assembly in Geneva, May 20-28, 2019 it was noted: «Patient harm due to adverse events is one of the leading causes of death and disability globally. An estimated 134 million adverse events occur annually due to unsafe care in hospitals in low- and middle-income countries, contributing to 2.6 million deaths, while 1 in 10 patients is estimated to be harmed while receiving hospital care in high-income countries». Member States meeting at the World Health Assembly committed to recognize patient safety as a key health priority, and to take concerted action to reduce patient harm in healthcare settings" [8]. Studies have shown that the risk of fatal outcome due to medical error or medical malpractice in tens, sometimes hundreds higher than the risk of dying in a car accident [9, p.878].

The system of international legal standards in the field of patient rights includes: 1) global and regional international human rights acts, in particular the Universal Declaration of Human Rights (1948), the European Convention on the Human Rights and Fundamental Freedoms (1950), the European Social charter (1961); 2) international documents on the patient rights and their provision, including Recommendations of the Council of Europe on the rights of the ill and the dying (1976), the Council of Europe Convention on the Protection of Human Rights and Dignity in the Application of the Achievements of Biology and Medicine (1996), Council of Europe Recommendations on the Control of Patient Safety and Prevention of Undesirable Effects in Health Care (2004); 3) acts adopted by international organizations designed to develop health standards, for example, the Lisbon Declaration of the World Medical Association on Patient Rights (1981), the Hawaiian Declaration II (Code of Ethics) of the World Psychiatric Association (1983). The central position of the patient in health care has been stressed in international regulations and set out in several specific treaties, regulations and directives such as the European Social Charter of the Council of Europe and the Declaration on the Promotion of Patients' Rights in Europe of the World Health Organization.

The document "Declaration on the promotion of patients' rights in Europe", by the WHO European Patients' Consultative Meeting (Amsterdam, March 28-30, 1994) [10] played an important role in defining key provisions in patient rights. The list of patient rights in this document reflects the progressive trends of today and corresponds to the development of modern law and health care. The purpose of this document is to guarantee the protection of fundamental human rights and promote the humanization of assistance to all categories of patients, including the most vulnerable, such as children, psychiatric patients, the elderly and severely ill. In essence, this reflects people's desire not only to improve the quality of their received treatment and preventive care, but also to more fully recognize their rights as patients.

The European Charter of Patients' Rights (2002) [11] states patients' rights to information on the diagnosis and prognosis of their own illness; the right to choose a doctor; the right to preserve the confidentiality of medical information; the right to privacy; the right to ensure the rule of informed consent, etc.

The above international acts contain standards that Ukraine must adhere to in the process of establishing norms and their implementation. An analysis of the domestic regulatory framework in the field under study will lead to the conclusion that the implementation and regulation of the patients' rights in Ukraine is disorderly, has a stratified character, which is due to a large number of legislative and subordinate acts (about 50). These regulations often include a set of general and special instructions that do not fully correspond to international standards either terminologically or content wise. One of the main factors contributing the lack of a single legislative regulation and unequal enforcement practice in this area is that Ukraine has not ratified the European Charter of Patients' Rights [7, p 54-55].

In 2011, under the framework of the Council of Europe Action Plan for Ukraine for 2011-2014 (approved by the Committee of Ministers of the Council of Europe on June 23, 2011) [12], the Ministry of Health of Ukraine with the participation of the All-Ukrainian Council for the Protection of Patients' Rights and Safety prepared a draft of National Plan of Action on patient safety. The purpose of the document is to improve the health of Ukrainian citizens by developing policies aimed at enhancing patient safety, preventing medical errors and reducing expenditures related to the inappropriate performance of the duties of managing patient safety and preventing incidents in the field of health care. However, the final version of the National Action Plan on Patient Safety has not been approved for today.

On January 1, 2012, the Law of Ukraine "Fundamentals of Ukrainian Legislation on Health Care" was supplemented by Article 24-1 "Protection of Patients' Rights" [13], according to which the legal, economic, and organizational foundations for the protection of the rights and legitimate interests of patients will be determined by a special law. But currently there are no such a special law in our state. The patients' rights require state guarantees through the formation of an effective public health policy, the establishment of an effective mechanism for their implementation, protection and legal provision. It is necessary to adopt a special law "On the Legal Status of Patients in Ukraine" as the basis for legal regulation of the status of a person when applying for or obtaining health care services.

However, according to international experience, if such norms are included in a single legal document, this helps more both the health care consumers to know their rights and those who are obliged to control and check them. So, there are different legislative technologies for summarizing patients' rights to a separate law, and they determine what this law will be: an administrative, civil or criminal one. Civil law provides the right to choose the horizontal contractual relationship between the patient and those who provide medical services. Countries such as the Netherlands and Lithuania has already used this model when drafting their patients' rights laws. Similar relationships between the patient and those who provide medical services exist in a system that regulates and controls the provision of general medical care services in France. In abovementioned countries patients with complains against doctors apply to a civil court. The government of countries such as Finland, Iceland and Denmark use an administrative law to protect patients' rights. In France, the legal rules governing the relationship between the patient and those who provide health care (provider) depends on the type of provider (doctor or health facility) [14].

In many countries of the European Union there is a charter of patients' rights. In countries such as France, Ireland, Portugal and the United Kingdom, it was adopted at the national level and sent to all health facilities. In the Czech Republic and Slovakia the charter has been designed and proposed by the healthcare institutions.

According to M. Watad and R. Grevtsova, "it is important that during the attempts to resolve various relationships related to human health, they have not forgot about the patient, the very person for whom these relations arise". An important instrument for ensuring this is the international medical law, which has a human-centric orientation [15, p. 460].

The patient rights in Ukraine are enshrined in a number of normative acts, in particular, in the Constitution of Ukraine, the Civil Code of Ukraine, the Laws of Ukraine "Fundamentals of the Ukrainian legislation on health care", "On consumer rights protection", etc. Scientists distinguish five groups of patient rights: 1) constitutional rights; 2) general rights of patients; 3) special rights of patients depending on the type of provided health care; 4) special rights of patients depending on the direction of medical activity; 5) special rights of various occupational and social categories of patients [16, p.179].

In particular, the second group "General Patients' Rights" covers the rights of all patients regardless of the type of health care, the doctor specialization, the direction of medical activity, professional, social or other characteristics of patients. The general patients' rights are more completely regulated by the norms of the Law of Ukraine "Fundamentals of the Ukrainian legislation on health care" [13] and the Civil Code of Ukraine [17]. The following rights of patients should be included in this group: 1) the right to qualified health care (Article 284 of the Central Committee, clause "d", part 1, Article 6 of the Fundamentals); 2) the right to choose a doctor, a medical institution, methods of treatment (Part 2 of Article 284 of the Civil Code, paragraph "d", part 1, Article 6, Article 38 of the Fundamentals); 3) the right to accurate and complete information about the state of health (Article 285 of the Central Committee, clause "e", part 1, Article 6, Article 39 of the Fundamentals); 4) the right to a secret about his/her health, the fact of applying for medical assistance, a diagnosis, as well as information obtained during a medical examination (Article 286 of the

Central Committee, Articles 39-1, 40 Fundamentals); 5) the right to informed consent for medical intervention or refusal of medical intervention (Article 289 of the Central Committee, Articles 42, 43 Fundamentals); 6) the right to be provided with medicine (in particular, immunobiological drugs) and prosthetic products (Article 54 of the Fundamentals); 7) the right to refuse treatment (Part 4 of Article 284 of the Civil Code); 8) the right to appeal against unlawful decisions and actions of employees, institutions and health care bodies (Article 6 of the Fundamentals).

The special rights of patients, in particular, in the field of transplantation of human organs and tissues, defined in Ukrainian Law "On Transplantation of Human Anatomical Materials", include the rights of living donors, a man who donate organs or tissue that are significantly expanded. In particular, it is right to: free health screening, directly related to the donation of anatomical materials; free medical aid in case of illness or health complications due to the donation of anatomical materials; advantage in obtaining anatomical materials in the event that there is a need of transplantation, etc. (Article 22) [18].

However, S.Bulecja points out that many patients' rights are not defined in the legislation of Ukraine, but are applied in medical practice, therefore, they require a legal regulation. In particular, they should include: the right to convene a consilium; the right to refuse medical interference; the right to terminate treatment. In addition, with the development of medicine, scientific and technological progress, there are some questions that need to be defined in legislation, among them the rights and responsibilities of the patient during transplantation, artificial insemination, medical examinations, etc [19.p.13].

The patients should be involved in the planning of treatment, on making changes and additions to the medical records relating to his health. The medical treatment of a patient should fully satisfy with his health requirements, should be conducted only for therapeutic or diagnostic purposes and not used as punishment or in the interests of others.

Furthermore, it is necessary to resolve the problem of regulating the rights and obligations of the patient and the doctor at the legislative level, including ensuring that the person is informed about the consequences of the exercise of such rights. Thus, in the EU countries, the relationship between a doctor and a patient has a civil law nature, because it is based on a civil contract between them. The realization of the right to health is based on the following principles: 1) the doctor and the patient are "partners" in achieving the goal (recovery of the patient), their relations are based on mutual trust; 2) high requirements to the professional level of the doctor, constant improvement of his professional qualities, high moral principles, 3) the right of the patient to choose a doctor, treatment methods, refusal of treatment, etc .; 4) the civil law (private law) nature of relations between the patient and the doctor; 5) the patient is obliged to adhere to all recommendations of the doctor [19, p.15].

The patient has the right to keep a secret about his/her health, the fact of applying for medical assistance, a diagnosis, and any other information that has become known to a medical practitioner or other person in connection with the performance of official duties, in the process of providing health care, to preserve the medical secret after the death of a person. For example, the jurisprudence of the European Community countries (in particular, Germany) proceeds from the fact that all data on the illness, family and intimate life of the deceased person are still the subject of medical secret in order to protect his good name and his relatives' reputation.

Due to the need to preserve human identity, to ensure respect for human dignity and the availability of a "bioethical dimension" of issues to be resolved by the legislator or the court, the impact of bioethics on the right to health is increasing. Some researchers focus on "bioethisation" of legislation and the rights of foreign countries in certain areas, for example, in the field of criminal law, and its necessity for Ukraine [20, p. 140-145].

One of the most acute problems is the consent of the patient to participate in a medical research (medical biologic experiment). On the one hand, there is a need to revise certain standards of research aimed at preventing abuse of consent, especially by consent of vulnerable persons (capable or incapable adults, minors). On the other hand, strict regulation of research, the trend of which has been observed lately, may lead to a restriction of research, despite the great role they play in meeting the needs of society in health care services. According to Y. Dangati, now it is necessary to establish a balance between the protection of the rights of the subjects and the ability to freely conduct research [21, p. 489].

At the same time there is a problem of medical error which is urgent not only for Ukraine. The high level of medical errors of formally high-qualified medical personnel is associated with the attestation system' bribability. At the same time, the qualification category does not mean that the doctor will be responsible. In Ukraine, there is no mechanism for prosecuting a specialist for incompetent provision of health care and medical treatment [22]. According to R. Hrevtsova, creating a system for reporting medical errors and monitoring them should be one of the priorities of health care reform in Ukraine [23]. The proposal of S. Dutchak is to supplement the Criminal Code of Ukraine with a norm that would include liability for the violation of patient rights by a medical or pharmaceutical personnel knowingly that could pose a threat to the life, health or reputation of a patient seems quite appropriate [7, p. 136].

The practice of the European Court of Human Rights, which has recently touched upon a fairly wide range of bioethical issues (reproductive rights, the use of assisted reproductive technologies, assisted suicide, consent) has played an important role in finding of legislative solutions to the problems posed by the right to health care. for medical intervention, etc.) [24], and also led to the spread of positive state obligations in healthcare, raising the issue of health care guarantees, government responsibility for patients' death, etc. [25, c. 15].

An analysis of practice of European Court of Human Rights indicates that the most widespread violations of patient rights are as follows: 1. ***Medical personnel are not able to provide the patient with information about the state of his health in an accessible form*** (*K.H. and Others v. Slovakia*), (Communication No. 32881/04 (2009); (*Roche v. United Kingdom*) (Communication No 32555/96), (2005). 2. ***Medical personnel ignore patients' wishes associated with the treatment*** (*Storck v. Germany*) (Communication No 61603/00), (2005), (*Aerts v. Belgium*), (Application No. 25357/94), (1998), *(R. R. v. Poland*), (Communication No 27617/04), (2011), (*Aerts v. Belgium*), (Application No. 25357/94), (1998), (*R. R. v. Poland*), (Communication No 27617/04), (2011). 3. ***Doctors either do not receive the informed consent of patients before performing medical procedures, or do not provide patients with information in an amount sufficient to make an informed decision*** (Glass *v. United Kingdom*) (2004); (*V.C. v. Slovakia*), (Communication No 18968/07) (2011)]; (*N.B. v. Slovakia*), (Communication No 29518/10), (2012); (*Y.F. v. Turkey*), (Communication No 24209/94), (2003)]; (*Pretty v. United Kingdom*) (2002)]. 4. ***Persons sentenced to imprisonment are not provided with emergency medical care*** (*Hurtado v. Switzerland*), 17549/90 (1994); (K*eenan v. United Kingdom*), 27229/95 (2001), (*Nevmerzhitsky v. Ukraine*), 54825/00 (2005)]; (*Musial v. Poland*), 28300/06 (2009), (*Rupa v. Romania*), 58478/00 (2008). 5. ***Patients with mental disorders are hospitalized in specialized institutions without clear procedure or standards*** (*X v. United Kingdom*) (1981); (*Gajcsi v. Hungary*) (Application No. 34503/03), (2006); (*H.L. v. United Kingdom*), (Application No.45508/99), (2004), (*Storck v. Germany*), (Application No. 61603/00), (2005), (*DeDonder and De Clippel v. Belgium*), (Application No. 8595/06), (2011).

Contrary to the practice of the ECHR, the national practice of litigation concerning the rights of patients is still in the process of developing because the number of such cases are few. According to V. Franchuk, approximately 600 cases of alleged medical malpractice cases are registered annually in Ukraine. Only less than one percent of them are brought to the court [26].

The ECHR has continued to note persistent non-compliance with the patient's rights in custody by Ukrainian authorities (*Salakhov and Islyamova v. Ukraine*) (application No. 28005*/08, decision (2013), Vitkovskiy v. Ukraine (application no. 24938/06, decision (2013), Akopyan v. Ukraine* (Application no. 12317/06) (2014). The lack of the necessary and timely treatment is seen as torture by the ECHR (*Lunyov v. Ukraine*) (Statement No. 4725/13) (2016).

Among the patient's rights, special attention should be paid to the right to safety. At the international level the patient's right to safety is recognized as one of the most important rights of the patient and is defined as "the right to freedom from harm caused by poor healthcare systems, negligence and medical errors" (European Charter of Patients' Rights, 2002). Yu. Kozachenko reasonably offers: "Unfortunately, the patient right to safety is not regulated by domestic legislation. Patient's safety should be one of the priorities of domestic medical institutions; it is necessary to legislate the concept of "patient safety" and establish clear aspects covered by the concept "patient right to safety" [16]. It is necessary to support the need to establish the concept of "patient safety" at the legislative level and to establish the contents of patient's right to safety.

S.Dutchak point out: "Today, the criminal law protection of patient's rights in Ukraine is ineffective. Most of the violations of the patient's rights remain latent or uninvestigated. And this is not only due to the mistrust that guilty doctors can be prosecuted, because of complicated procedures for proving the guilt of medical workers, but also due to improper criminal formulation and detailization of the nature of the patient's rights violations, which makes the offenders non-punishable" [7].

According to the Unified State Register of Judgments from 2009 in Ukraine, under the Article 141 of the Criminal Code of Ukraine, which provides liability for the violation of patient's rights, have not been handed down any sentences. According to Article 140 of the Criminal Code of Ukraine (improper performance of professional duty by a member of medical profession) - 44 sentences. Analysis of court practice on Article 140 of the Criminal Code of Ukraine in the past 10 years permits the following conclusions: 1) the majority of sentences are imposed in part 1 of Art. 140 of the Criminal Code of Ukraine; 2) several sentences were issued under Part 2 of Art. 140 of the Criminal Code of Ukraine, but the guilty persons were released from serving the sentence, including in cases of death of minors; 3) the proportion of acquittals sentences under art. 140 of the Criminal Code of Ukraine is very insignificant (4, 5%).

The penalties provided in Article 140 of the Criminal Code of Ukraine is too lenient particularly in cases where such serious consequences for the patient as his death occurs. (For example, the verdict in the case No. 456/310/18 of April 24, 2019, before the court of Lviv region under part 1 of Article 140 of the Criminal Code of Ukraine) [27].

During this period, only a few sentences were pronounced under Part 2 of Art. 140 of the Criminal Code of Ukraine, but the guilty persons were released from serving the sentence. Thus, in the Case No. 1-73-09, heard in 2009 in the Volyn region, the person was found guilty of improper performance of his professional duties due to careless attitudes towards them that caused the death of a minor and she was convicted and sentenced to three years of imprisonment with the deprivation of the right to hold the position of a nurse in health care facilities for a term of three years. Under Article 75 and 76 persons was released from serving principal penalty [28]. In another case No. 214/6891/17 dated January 8, 2019, the person who has been convicted of a criminal offence, under Part 2 of Art. 140 of the Criminal Code of Ukraine, consequence of which was death of a minor and she was appointed to a primary penalty of 2 years imprisonment. Under Art. 75 of the Criminal Code of Ukraine the court decided to exempt the person from release a person from serving her primary penalty [29].

The protection of patients' rights should be implemented, in particular, by compensation for moral harm, which is paid regardless of age, health, property status. The court, when awarding compensation, must assess the depth of moral suffering, taking into account the factual circumstances in which the pecuniary damage was committed and the individual characteristics of the victim. However, it is advisable to determine the upper and lower limits, taking into account the severity of the emotional distress. Interesting in this respect is ruling of the Supreme Court of 08 May 2019 № 233/3464/17 according to the protocol of the medical examination, which has been formulated with significant deficiencies recognized ground for reimbursement by medical institution for moral injury in the amount of 100000 UAH per each of the plaintiffs [30].

According to V. Tatsiy, N. Gutorova, V. Pashkov, formation of a state policy on ensuring the rights of citizens to health and life, taking into account the various consequences of such a policy, cannot be narrowed down only to the proclamation of such rights, but also requires planning and development of relevant state programs [31]. An important element of the patient rights promotion system is standardization of health care, the ultimate goal of which is its quality and safety.

CONCLUSIONS

1. Adaptation of the Ukrainian legislation to the the European Union legislation is an important direction of reforming the domestic legislation in the field of ensuring the patient rights and bring it in line with international standards. Taking into account foreign experience in the field of patient's rights provision, it is necessary to adopt a special law "On the Legal Status of Patients in Ukraine" as the basis for legal regulation of the status of a person when applying for or obtaining health care services.
2. When making health policy, the concept of trust and respect for patients, their autonomy or constructive partnership with them should be taken into account. Doctors need to take a more active part in discussions and debates with patients. Independence of patients in decision making processes must be provided by law.
3. In Ukraine's legislation wide range of patient's rights are not defined, but are applied in medical practice, therefore, they require legal regulation. In particular, they are: the right to convene a consilium; the right to refuse medical interference; the right to terminate treatment. In addition, with the development of medicine, scientific and technological progress, there are questions that need to be defined in the legislation, among them the rights and responsibilities of the patient during transplantation, artificial insemination, medical research, etc. It is necessary the need to establish the concept of "patient safety" at the legislative level and to establish the contents of patient right to safety.
4. Contrary to the practice of the ECHR, the national practice of litigation concerning the rights of patients is still developing because the number of such cases are few. The ECHR has continued to note persistent non-compliance with the patient's rights in custody by Ukrainian authorities. The lack of the necessary and timely treatment is seen as torture by the ECHR.
5. It is necessary to resolve the problem of regulating the rights and obligations of the patient and the doctor at the legislative level, including ensuring that the person is informed about the consequences of the exercise of such rights.

REFERENCES

1. Pasjko MI. Osoblyvosti nadannja medychnoji dopomoghy ta medychnoji poslughy v umovakh formuvannja rynku medychnykh poslugh [Particularities of Rendering Medicare and Medical Service in the Conditions of Services Market's Formation]. Global and National Problems of Economics (online). 2017;15:117–121 [download: 12.04.2019]; http://global-national.in.ua/issue-15-2017/23-vipusk-15-lyutij-2017-r/2742-pasko-m-i-osoblivosti-nadannya-medichnoji-dopomogi-ta-medichnoji-poslugi-v-umovakhformuvannya-rinku--poslug. (In Ukrainian).
2. Babadjanov Dj. Ponyatie pacienta v teorii i zakonodatelstve [The Notion of "Patient" in Theory and Legislation]. Bulletin of the Tajik State University of Law, Business and Politics. Series of Humanitarian Sciences. 2014;5(61):63–68. (In Russian).
3. Pishita AN. Pravovoe regulirovanie medicinskoj deyatelnosti v sovremennoj Rossii: teoretiko-pravovye aspekty [Legal regulation of medical activity in modern Russia: theoretical and legal aspects]. Moscow: TsKB RAN; 2008. (In Russian).
4. Samilyk LO. Pravovyj status sub'jektiv medychnogho prava [The Legal Status of the Subjects of Medical Law]. Porivnjaljno-analitychne pravo (online). 2018;1:111–114 [download: 12.04.2019]; http://www.pap.in.ua/1_2018/31.pdf. (In Ukrainian).
5. Kutuzova D, Stepurko T, Kovtoniuk P. Pacijent, spozhyvach chy klijent? Jak nazyvaty tykh, khto po cej bik likarni? [Patient, Consumer or Client? Who Are Those who Are Outside of the Hospital?]. NaUKMA Research Papers. Sociological sciences. 2015; 174:86–91. (In Ukrainian).
6. Parsons T. The sick role and the role of the physician reconsidered. The Milbank Memorial Fund Quarterly. Health and Society. 1975;53(3):257–278.
7. Dutchak SR. Zabezpechennja okhorony prav pacijenta v Ukrajini: kryminaljno-pravovyj aspekt: dys. … kand. juryd. nauk [Ensuring the protection of patient rights in Ukraine: the criminal-law aspect: Candidate's thesis]. Kyiv; 2018. (In Ukrainian).
8. World Health Assembly Update, 25 – 29 May 2019 - News release, Geneva [download: 29.05.2019]; https://www.who.int/ru/news-room/detail/25-05-2019-world-health-assembly-update
9. Alesia Gornostay, Alona Ivantsova, Tetiana Mykhailichenko Medical error and liability it in some post-Soviet countries (Belarus, Kazakhstan, Moldova, Ukraine) Wiad Lek 2019, 72, 5 cz. I, 877-882, tom LXXII, nr 5 cz I, p.878.
10. Declaration on the promotion of patients' rights in Europe [download: 29.05.2019]; https://www.who.int/ru/news-room/detail/25-05-2019-world-health-assembly-update/
11. The European Charter of Patients' Rights. Rome, November http://ec.europa.eu/health/ph_overview/co_operation/mobility/docs/health_services_co108_en.pdf
12. Plan diy Rady Yevropy dlya Ukrayiny na 2011 - 2014 roky vid 23 chervnya 2011 roku [Plan for Ukraine for 2011-2014 dated June 23, 2011] [download: 23.05.2019]; https://zakon.rada.gov.ua/laws/show/en/994_b25

13. Osnovy zakonodavstva Ukrajiny pro okhoronu zdorov'ja: Zakon Ukrajiny vid 19.12.1992 r. № 2801-XII [Fundamentals of Ukrainian Health Care Legislation: Law of Ukraine dated December 19, 1992 No. 2801-XII]. Vidomosti Verkhovnoi Rady Ukrainy. 1993;4:19 [download: 12.04.2019]; https://zakon.rada.gov.ua/laws/show/2801-12. (In Ukrainian).
14. Parashhych IM. Prava pacijentiv: problemy jikh vyrishennja (dosvid krajin Jevropejsjkogho Sojuzu) [Patients' rights: the problems of their solution (experience of the countries of the European Union)]. Ekonomika ta derzhava. 2009;5:78–80. (In Ukrainian).
15. Wattad MS, Hrevtsova R. Reflections on International Medical Law. The International Journal of Medicine and Law. 2011;30(4):449–460.
16. Kozachenko YuA. Pytannja systematyzaciji prav pacijenta [To the Question of Systematization of the Patient's Rights]. Problems of Legality. 2014; 125:177–183. (In Ukrainian).
17. Cyviljnyj kodeks Ukrajiny: Zakon Ukrajiny vid 16.01.2003 r. № 435-IV [Civil Code of Ukraine: Law of Ukraine dated January 16, 2003 No. 435-IV]. Kharkiv: Pravo; 2019. (In Ukrainian).
18. Pro zastosuvannya transplantatsiyi anatomichnykh materialiv lyudyni: Zakon Ukrajiny vid 17 maya 2018 No.2427-VIII [On Transplantation of Human Anatomical Materials: Law of Ukraine dated May 17, 2018 No.2427-VIII]. Vidomosti Verkhovnoi Rady Ukrainy. 2018; No. 28, p.232. (In Ukrainian).
19. Bulecja SB. Pravo fizychnoji osoby na zhyttja ta zdorov'ja jak ob'jekt cyviljno-pravovoji reghlamentaciji: porivnjaljno-pravovyj analiz reghuljuvannja v Ukrajini, Ughorsjkij, Slovacjkij ta Chesjkij respublikakh: avtoref. dys. … kand. juryd nauk [The right of an individual to life and health as an object of civil legal regulation: a comparative legal analysis of regulation in Ukraine, the Hungarian, Slovak and Czech Republics: Extended abstract of candidate's thesis]. Odesa; 2005. (In Ukrainian).
20. Trinova YaO. Bioetychni problemy kryminaljnogho prava Ukrajiny: monoghrafija [Bioethical problems of the criminal law of Ukraine: monograph]. Kyiv: National Academy of Prosecutor's Office of Ukraine; 2014. (In Ukrainian).
21. Dangata Y. The Role of Consent in Medical Research: Breaking or Building Walls? A Call For Legislative. Med Law. 2011;30(4):477–495.
22. Yuridicheskaya otvetstvennost vrachej budet rasti uzhe v etom godu [The legal responsibility of doctors will grow this year. Protocol: legal Internet resource]. 2019 Jan 21 https://protocol.ua/ua/yuridicheskaya_otvetstvennost_vrachey_budet_rasti_uge_v_etom_godu(In Russian).
23. Hrevtsova R. U vsjomu sviti «medychni» spravy vvazhajutjsja odnymy z najskladnishykh [Worldwide, «health» cases are considered one of the most difficult]. Law and Business (online). 2017;31(1329) [download: 12.04.2019]; https://zib.com.ua/ua/129800-golova_komitetu_aau_radmila_grevcova_u_vsomu_sviti_medichni_.html. (In Ukrainian).
24. Bioethics and the case-law of the Court: Research report. 2012 May https://www.coe.int/t/dg3/healthbioethic/texts_and_documents/Bioethics_and_caselaw_Court_EN.pdf.
25. Buzadzhi KM. Konvencija pro zakhyst prav ljudyny i osnovopolozhnykh svobod ta pytannja medychnogho prava v Ukrajini [Convention on protection of Human Rights and Fundamental Freedoms and the question of health law in Ukraine]. First All-Ukrainian Congress on Medical Law and Social Policy: a Collection of Abstracts April 14-15, 2007. Kyiv; 2007:15–16. (In Ukrainian).
26. Franchuk VV, Trach Rosolovska SV, Selskyy PR, Mykolenko AZ, Bodnar PY. Analysis of final judgements in cases of medical negligence occurred in Ukraine. Wiad Lek. 2018;71(3 pt 2):757-760.
27. Vyrok u spravi № 456/310/18 vid 24 kvitnya 2019 roku [Verdict in the case No. 456/310/18 of April 24, 2019] [download: 12.05.2019]; https://youcontrol.com.ua/catalog/court-document/81246509/ (In Ukrainian).
28. Sprava N 1-73-09 (2019) [Case No. 1-73-09 (2019)] [download: 15.05.2019]; http://www.reyestr.court.gov.ua/Review/3906731 (In Ukrainian).
29. Sprava N 214/6891/17 (2019) [Case No. 214/6891/17 (2019)] [download: 16.05.2019]; http://www.reyestr.court.gov.ua/Review/79063650 (In Ukrainian).
30. Postanova Verkhovnoho Sudu vid 8 travnya 2019 roku u spravi № 233/3464/17 [Resolution of the Supreme Court dated May 8, 2019 in the case No. 233/3464/17] [download: 12.04.2019]; http://www.reyestr.court.gov.ua/Review/81753098. (In Ukrainian).
31. Tatsiy V, Gutorova N, Pashkov V, Legal aspects of cancer deseases prophylactics: patients rights context. Wiad Lek. 2017;70(6 pt 1):1108-1113.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Tetyana Vilchyk
Yaroslav Mudryi National Law University
tel: +380679727453
e-mail: Kafe-agata@i.ua

Received: 15.03.2019
Accepted: 17.06.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

SPECIFIC ASPECTS OF NORMATIVE LEGAL REGULATION OF ANATOMICAL MATERIALS' TRANSPLANTATION IN UKRAINE AND FOREIGN COUNTRIES

Marina M. Novytska
SUMY STATE UNIVERSITY, SUMY, UKRAINE

ABSTRACT

Introduction: The article is devoted to the research of normative regulation of human organs and tissue transplantation in Ukraine and some foreign countries. A considerable part of problem aspects of transplantology in Ukraine is hidden due to the normative and legal base shortcomings, therefore there is a necessity of considering and borrowing foreign experience of legal regulation of this process, a legal regulation of the bases and conditions of providing consent to the removal of organs or refusal of the potential donor and legal consequences of it. The question as for the possibility of consolidating the "consent presumption" on the removal of organs and tissues at the legislative level remains current, but many experts express the idea of inadmissibility of such legislative actions because of the military operations on the territory of Ukraine and the imperfection of state control for the activities of institutions performing transplantation. At the same time, it is obvious that now the legislative regulation of the sphere of transplantology does not meet modern requirements, and creates certain gaps in the Ukrainian legislation.

The aim is to determine and concretize problematic issues of legal regulation of the transplantation sphere in Ukraine, to analyze the experience of the successful countries in this direction and to develop an integrated approach to the solution of certain problems.

Materials and methods: During the research, international normative acts, national legislation acts and scientific works of scholars were used. The article is based on the dialectical, legal, historical, comparative, systematic methods of research.

Review: The analysis of the current situation of legal regulation of the sphere of transplantology in Ukraine has been carried out, the main problems and gaps, which must be eliminated as soon as possible for the real possibility of organ and tissue transplantation operations, are identified. The experience of the most progressive countries that are leaders in the number of transplantation operations is analyzed and their experience has been taken.

Conclusions: The solution of this problem is possible only after the transformation of the transplant coordination system, the introduction of the Unified State Information System for transplantation, the training of specialized personnel, the improvement of the technical equipment of medical institutions, and the creation of an effective mechanism for regulating of the human anatomical materials' transplantation.

KEY WORDS: transplantation, transplantation of organs, anatomical materials, medical law

Wiad Lek 2019, 72, 7, 1331-1336

INTRODUCTION

The health of each person is the key to the prosperity of any nation. That is why in the conditions of modern medical reform in Ukraine it is vital to preserve the life of patients and provide them with high-quality medical services, the basis of which is reasonable and coordinated activity of the state in support of the Ukrainians' health. Now, the issue of organs and other human anatomical materials' transplantation as a modern highly effective method of treating of serious illnesses in severe stages of organ failure is very acute. Medicine is constantly developed evolving and renewing the new ways of human life rescue, but the imperfection of the legislative base and the lack of a system of concerted actions significantly slow progress in the field of transplantology. A large number of scholars in their works emphasized the necessity of the fastest reforming of the legislation in the field of transplantology in accordance with international standards, namely: V.A. Glushkov, S.V. Grynchak, D.P. Kobyakova, N.A. Margatska, I.V. Mishchuk, O.G. Pelagesha, S.S. Tikhonova, B.M. Todurov, V.I.Shumakov and others. However, despite the huge transplantation needs (more than 6,000 operations per year), the profound work of scientists in this field and the huge public response caused by the daily necessity for organ transplantations, the number of such operations is negligible. And even the adoption of the new Law of Ukraine "On the application of transplantation of anatomical materials to a human being " (hereinafter - the new law) [1] May 17, 2018, did not improve the situation in the country, but on the contrary - complicated it for a while, and even blocked the operations from a family donor. The level of transplantology development is an indicator of the successful work of public authorities in maintaining the quality of health care, as well as the degree of the country development in general. The field of transplantation has a long way from the medical experiment (as it was at the early beginning) to the traditional and routine manipulation in medical practice of highly developed countries, but in our coun-

try, unfortunately, it is not the same, because today there is a wide range of legal issues, procedures, administrative bodies are not regulated by the legislation of Ukraine yet.

THE AIM

The aim is to determine the current status of normative and legal support of the transplantology in Ukraine, coverage of its main gaps and collisions, as well as comprehensive and profound analysis of normative acts of certain foreign countries as for human anatomical materials' transplantation in order to understand their conceptual provisions and possibilities of taking into account and further realizing (using) the positive experience of these developed countries.

MATERIALS AND METHODS

To achieve this objective, a set of research methods is used, in particular: comparative, dialectical, historical, systemic, logical, formal-legal, method of modeling, quantitative-qualitative, studying of documents, generalization method.

REVIEW AND DISCUSSION

The development of world medicine and transplantology, in particular, has reached such heights when specialists have the opportunity to transplant almost any organ, they try to create not only a part, but also a whole body on a 3D printer; flying drones, which themselves deliver anatomical materials to your destination, were created. And it is only an insignificant part of those science's achievements that will become available to patients who need organ transplantations and / or tissue. Transplantology is the branch of medicine which is the most promising and dynamically developing. In a global scale, now there are more than 1 million people who were transferred organ transplantation and have an active lifestyle.

Worldwide growth rates of transplantation operations suspect that in 15-20 years, up to 60% all surgeries will be followed by organ transplantation, tissues, cells and bioimplants (including xenotransplantations) [2, p.88]. Considering such significant world progress in the sphere of transplantology the Ukrainian realities seem to be more miserable. The reason for the decline of this branch of medicine is also in its long-term ignoring by the Ukrainian law. After all, the previous law regulating the sphere of transplantation "On organs and other anatomical materials transplantation to a human being" [3] was adopted in 1999 and since that time has not been practically changed. A new transplantation law was passed in 2018 thanks to a significant social impact of activists, public figures and doctors. Its adoption was a significant step forward in standard regulation of the transplantation sphere; however, it caused a significant number of unresolved issues for the state authorities. Among them: the absence of the Unified State Information System of Transplant Coordination (software and subordinate statutory acts that regulate its functioning); the uncertainty of cross donation usage in practice; the absence of a procedure of entering of a mark into the citizen's passport (driving license) or the issuance of a separate document confirming the consent of a person to be the organs donor; the lack of qualified and trained transplant- coordinators; the problem with licensing about transplantation; the absence of a central executive authority that implements state policy in the field of the provision of medical care with transplantation and the implementation of transplant-related activities; the uncertainty about the procedure of obtaining the consent from relatives of a potential donor, etc.

In order to resolve procedural issues which made impossible any transplantation after adoption of the new Transplant Act of January 01, 2019 and to "unblock" at least transplantations from a family donor (they were impossible due to the requirement of a new law about the inclusion of all information, concerning the transplantation to the Unified State Transplantation Information System which was not created),the Resolution of the Cabinet of Ministers was adopted of December 27, 2018, No. 1211 (came into force on February 13, 2019) "Some issues of the implementation of the Law of Ukraine "On transplantation of human anatomical materials "[4]. However, this Resolution was strongly criticized because it is impossible to change the procedure established in the law or to interpret its standards by means of a subordinate statutory act, such as a resolution of the Cabinet of Ministers of Ukraine.

That is why, under the public pressure on February 28, 2019, the Verkhovna Rada of Ukraine adopted the Law No. 2694-VIII "On amendments to some legislative acts of Ukraine as for anatomical materials' transplantation to a human being" [5]. This document introduced a number of significant amendments to the new transplantation law:

- the introduction of the Unified State Transplantation Information System (USTIS) was postponed until January 1, 2020 (until now, the transplantation organization will be based on paper information);
- the decision on the possibility / impossibility of the transplantation of anatomical material to the recipient from the donor -corpse is made by a consensus of doctors of the health care institution, according to the letter (waiting list) of which the recipient is included, according to the order of priority;
- before determining the qualification characteristics of transplantation coordinators, in health care institutions it is possible to appoint to such position by issuing an appropriate order to persons who will perform such functions;
- the authority of the customer of medical services was removed from the central executive authority, which implements the state policy in the field of the provision of medical care with transplantation and the activities related to transplantation (by the time of its creation and normative regulation of activities);
- the list of organizations and provision of medical care with transplantation and the activities related to transplantation is supplemented by the National Health Service of Ukraine (NHSU);

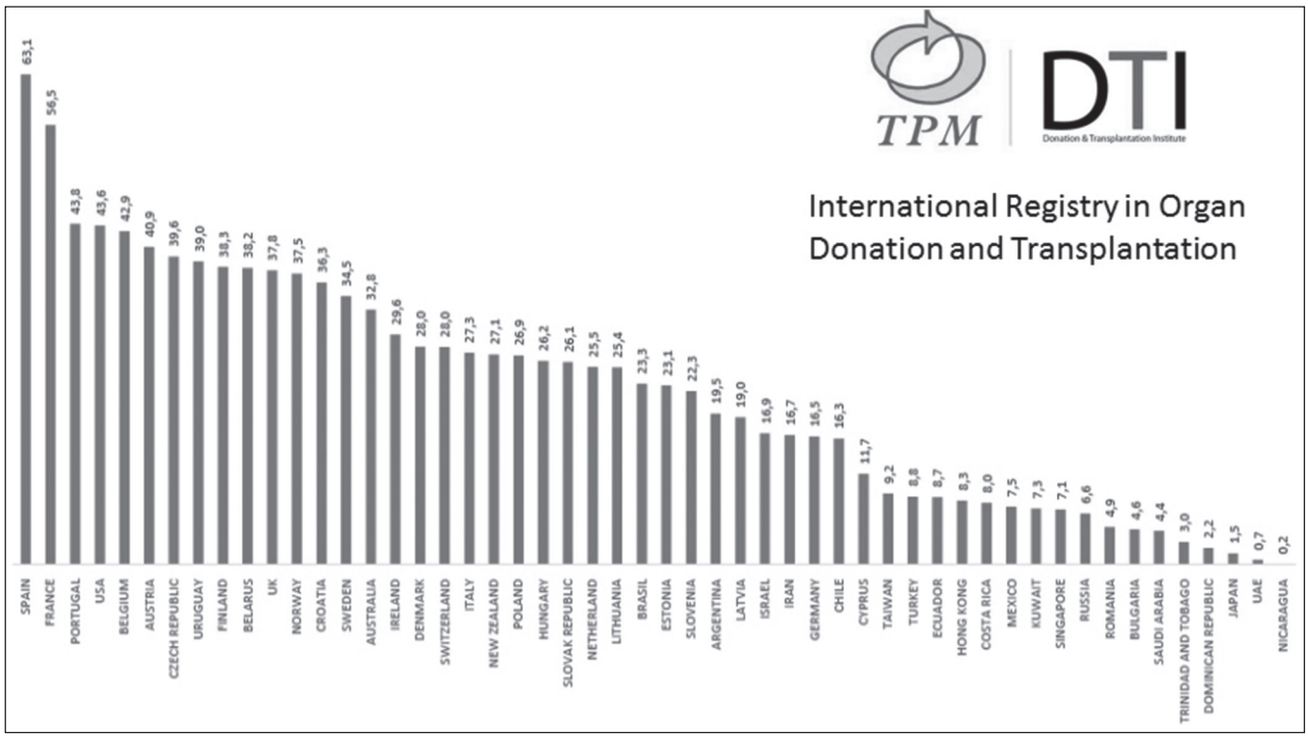


Fig.1. Report of the International Registry in Organ Donation and Transplantation for June 2018 [19].

- the term "activities related to transplantation", which includes removal, transportation, storage of anatomical materials, transplant-coordination, is established as a medical service (it will give the opportunity to pay for such NHSU services in the context of a guaranteed package of medical services);
- the list of persons who are close relatives is expanded; the following list is added: cousins, uncles, aunts, nephews, (it will expand the circle of persons for family donation);
- it is established that the family doctor will be able to obtain the consent for post-mortem donation and will have the right to submit such information to the Unified State Transplantation Information System;
- the possibility of donation of bone marrow from siblings aged up to 18 years;
- it specifies the fact that only free international exchange of anatomical materials is allowed; the exceptions are hemopoietic stem cells stem cells, their purchase and sale are allowed;
- the amendments have been made to Article 290 of the Civil Code of Ukraine, it is given the right to donate hemopoietic stem cells to persons aged up to 18 years in cases provided by the law [5].

However, the most essential barrier to the development of the transplantation sphere in Ukraine is the continuation of the presumption of disagreement ("*opting in*") - (it also operates in the United States, Britain, Germany, Canada, Greece, Japan – it means that a person's organs with a diagnosis of clinical death will be removed for transplantation only if he or she agreed during the lifetime to be an anatomical donor in case of the death). Any attempts to change the concept to another one - the consent presumption "*opting (or contracting out*)" - (it also operates in Austria, Denmark, Belgium, Spain, Kazakhstan, Belarus, Russia – it means that everyone can become a potential donor, if during the lifetime they did not write a refusal to ban the transfer of their organs) were strongly criticized.

Such negative attitude from the opponents of the new concept is justified by the possible violation of the right of the person to the integrity and inviolability of the body, as well as non-compliance with the priority of the people rights above the needs and interests of a society. Besides, fears of a possible growth in the criminalization of this branch of medicine (the risk of trading by human organs). It was claimed that this concept is a significant violation of human rights (donor), who during the lifetime had to decide about the possibility of using his or her own organs or tissues after the death. After heated discussion on this subject, it was decided that the Ukrainian public space was not ready for such changes; in spite of that fact the change of concept would influence the solution of the problem with donor organs 'deficits [2, p. 90].

The number of organ transplantations in the world for 1 million people (kidney, liver, heart, lung, and pancreas) is evidenced in favor of the "consent presumption" (e.g., Figure 1).

As you can see, *Spain* is the leading country in the number of transplantations. A new transplantology law was issued in Spain in 1979 [6]. It contained several important articles and a set of specifications. It is the law that plays a decisive role in the Spanish transplantation system. It details all the nuances connected with both the donor and

the recipient. It is noted that the recipient's family should not know who was a donor in case of corpse donation, as well as accurately pointed out doctors of whom specialties should record the donor's death. In 1982, the law was amended to require coordination centers to be set up in all medical institutions that are intended to be transplanted. Now there are the following levels of coordination: the first is the national organization of transplantology; the second one is the regional (17 regional coordination centers); the third one is hospitalized. The last two levels interact with the support of post-mortem donation. Any national decision about donation and transplantation in Spain is agreed with the Transplantation Commission of Health Care of the Interterritorial Council. It is the third-level coordinators who play a key role in increasing the number of donor organs from the died donor. The creation of such positive social climate towards donation and trust in society is achieved by close work with the media.

Not less considerable are the achievements of *Belarus* in the field of transplantation, where during the last eight years the rapid development of the number of organ transplantation operations is marked. The Law "On the human organs and tissues transplantation" [7] stipulates (in Article 10-1) the concept of consent. The significant achievements of the Belarusian legislation are the established and consolidated clinical protocols of kidney and heart transplantation; hematopoietic stem cells of adult patients; cornea, sclera of amniotic membrane; autologous and allogenic skin; the liver, are fixed by the Order of the Ministry of Health Care of 05.01.2010 No. 6 "On the Approval of Certain Clinical Protocols of the Human organs and tissues Transplantation" [8]. The protocols identify procedural actions after the diagnosis of brain death and recognition of the person as a "potential donor". There is an extensive transplant- coordination system and the Unified Register of Transplantation. Much attention is paid to normative regulation of the technical equipment of hospitals, material stimulation of doctors- transplantologists [9, p. 143].

There is a fixed approach of obtaining consent in *France* similar to the Ukrainian. According to Art.L1211-2 of the French Code of Health Care (Code de la sante publique) [10] the removal of human organs and tissues is not permitted without the prior consent of the donor, which (consent) can be withdrawn at any time. Moreover, according to Art. L1232-1, L1232-2 and other articles of the French Code of Health Care, the removal of organs and tissues from the corpse may also be carried out with the consent of the close relatives. The recipient's person should not be known to the donor and vice versa. No reward can be given to someone who alienates parts of his body and is ready for organs transplantation. In the case of life-time donations, the donor may be a recipient's mother or father. As an exception, it is permitted to involve as a donor a wife, husband, brother or sister, their own sons or daughters, grandparents, uncle's organs, cousins, as well as the wife of the father or a mother's husband. [11, p. 166].

In *Germany*, in the Federal Law "About the donation, search and transfer of organs and tissues" (short title – Transplantation Law) [12] of November 5, 1997 (with the following changes), in section 1, § 3, "Withdrawal with the consent of the donor" it is established that the removal of organs or tissues, unless otherwise specified in Sections 4 and 4a, is permitted only if: 1) there is a consent of the donor for the removal of organs or tissues; 2) the death of organs or tissues of the donor is established in accordance with the established rules; 3) the procedure is done by the doctor. According to sections 1, 2, §3 of this Law, the removal of organs or tissues is unacceptable if a person whose death is established denied the removal of an organ or tissue. In this case, the doctor should inform the close relatives of a potential donor of organs or tissues about the alleged removal of the organ or tissues. These persons have the right to decide about the sequence and extent of the organ or tissue removal. The closest relative has the right to control the removal procedure either himself or through a trustee appointed by him (Section 3 § 3). According to Section 1, § 4 of the German Law, the consent to the removal of organs or tissues from a cadaverous donor may be given by the family members. In the died person did not give the written consent to the removal of organs or tissues or written objections against becoming a donor of organs or tissues, the nearest relatives should be asked whether they know anything about the will of the died person in relation to the donation of organs and tissues. If such will of the died is unknown, organs or tissues removal can be done with the consent of the close relatives.

The *Belgian Law* about the removal and transplantation of organs says that the consent of the donor must be expressed in writing and signed in the presence of a capable witness. Several alternative forms of the donor's consent are specified in the *Greek Law*: a written form with a notaries certificate, a written form with a donor signature in the police and an oral form of consent in the presence of two witnesses with a record in the special register. The legislation of Belgium and Turkey requires the consent not only from the donor but even from his wife.

Donor issues in the *UK* are governed by statute laws. The first in this field are the Human Tissue Act of 1961 and the Organs and Cornea Transplants Act of 1952. These early acts regulate the removal and use of tissues and organs from a died person. Now the current legislation regulates the disposal, storage, and use of corpses and parts of corpses for transplantation and establishes a "presumption of disagreement" in the Human Organ Transplants Act of 1989 [13].

Having analyzed the legislation of foreign countries and the basic principles on which their normative acts in the field of transplantation are based, it should be noted that it is necessary to implement a number of fundamental international acts which are the foundations of human anatomical materials' transplantation for the implementation of international experience in the legislation of Ukraine.

According to the Ukraine's European integration direction and the Association Agreement [14], our state has undertaken a number of commitments to bring domestic legislation closer to European standards in the field of public health. In particular, in accordance with the "Plan

of Implementation of the Association Agreement between Ukraine, on the one hand, and the European Union, the European Atomic Energy Community and their Member States, on the other hand" [15], before 2017, three EU directives should have been implemented:

- Commission Directive 2004/23 / EU of the European Parliament and of the Council of 31 March, 2004 setting standards of quality and safety for the donation, receiving, testing, processing, preservation, storage and distribution of human tissues and cells (hereinafter referred to as Directive 2004/23 / EU) [16];
- Commission Directive 2006/17 / EU of 8 February, 2007 laying down the rules for the implementation of Directive 2004/23 / EU of the European Parliament and of the Council as for certain technical requirements for the donation, receiving and testing of human tissues and cells (hereinafter referred to as Commission Directive No. 2006/17 / EU) [17];
- Commission Directive 2006/86 / EU of 24 October, 2006 implementing Directive 2004/23 / EU of the European Parliament and of the Council as for monitoring requirements, notification of serious negative reactions and events, and certain specific technical requirements for coding, processing, storage, stockpiling and distribution of human tissues and cells (hereinafter referred to as Commission Directive 2006/86 / EU) [18].

All three Directives are in force and have not been replaced by other Directives. At the same time, the Directive No. 2004/23 / EU are "basic" and the other two are adopted by the European Commission for its implementation.

In view of these directives, in May 2018, the Ministry of Health Care committed to develop and adopt a number of regulations, as well as to ensure the functioning of the transplantation sphere before the beginning of 2019.

CONCLUSIONS

Based on the analysis of today's normative and legislative acts and the implementation plan of the Directives, it can be confirmed that the Ukrainian legislation reflects only the individual requirements of the given Directives. At the same time, a number of issues is not implemented to the Ukrainian legislation. In particular, this concerns the question of confidentiality. Also, the Ukrainian legislation should be done in accordance with the given Directives in relation to the introduction of a quality system in institutions working with human tissues and cells. In addition, it is necessary to add the criteria of selecting donors, to complete the standards for the preparation of tissues and cells, their processing and distribution of the direct supply of individual tissues and cells to the recipient, and, in general, to ensure the requirements 'compliance with the quality and safety of tissues and cells in Europe.

The imperfection of the current legal field of transplantology in Ukraine binds doctors' hands and creates the basis for the decline of the transplantation. That is why it is necessary to turn to the experience of foreign countries and to introduce a "consent presumption" at the legislative level. In countries where this concept is fixed there is no shortage of donor organs. According to the author, with the full awareness of citizens about the existing policy in the state and giving them an unhindered free opportunity to refuse to be a donor after death, this concept is not as negative as some scientists are trying to show it.

Due to such critical situation with the transfer of anatomical materials and in view of the European integration course of our country, Ukraine should borrow and implement the successful experience of foreign countries to create a truly effective system of transplantation.

REFERENCES

1. On the application of transplantation of anatomical materials to a human being: The Law of Ukraine, from May 17, 2018, No. 2427-VIII. Voice of Ukraine. 2018, № 115.
2. Marina Novitskaya, The comparative characteristics of legislation in the field of transplantation of organs and tissues in Ukraine and the Republic of Belarus. Legea și viața. Publicație științifico-practică. 2018;11/2:88-93.
3. On transplantation of organs and other anatomical materials to a human being: The Law of Ukraine, from July 16, 1999, No. 1007-XIV. Voice of Ukraine. - 17.08.1999.
4. Some issues of the implementation of the Law of Ukraine "On the Application of Transplantation of Anatomical Materials to a human being": Resolution of the Cabinet of Ministers of Ukraine dated December 27, 2018 No. 1211 / Cabinet of Ministers of Ukraine. URL: https://zakon.rada.gov.ua/laws/show/1211-2018-%D0%BF?lang=en.
5. On amendments to certain legislative acts of Ukraine regarding the application of transplantation of anatomical materials to a human being The Law of Ukraine No. 2694-VIII from February 28, 2019. Voice of Ukraine. - 2019 - No. 62.
6. Ley 30/1979, De 27 De Octubre, sobre extraccion y transplante de organos [Law 30/1979, of October 27, On organ extraction and transplant]. – URL: http://www/ont.es/infesp/Paginas/LegislacionBasica.aspx. (In Spain).
7. On transplantation of organs and tissues to a human being: Law of the Republic of Belarus, March 4, 1997, No. 28-3. Consultant Plus. Belarus. ООО "YurSpectr", National.center of legal inform. Resp. Belarus - Minsk, 2017.
8. Approval of some clinical protocols for the transplantation of human organs and tissues: Order of the Ministry of Health, January 5, 2010, No. 6. Consultant Plus. Belarus. ООО "YurSpectr", National.center of legal inform. Resp. Belarus - Minsk, 2017.
9. Marina Novytska, Transplant coordination in Ukraine: current state and development prospects. Visegrad Journal on Human Rights. 2018;6:140-145.
10. Code de la santé publique [Public Health Code]. URL: http://www.legifrance.gouv.fr. (In French).
11. The French Civil Code. Scientific. edit and the prelude D.G. Lavrov; per. A.A Zhukov - St. Petersburg: Yurid. Center Press, 2004,1101 p.
12. Gesetz über die Spende, Entnahme und Übertragung von Organen und Geweben (Transplantationsgesetz – TPG) [Law on the donation, removal and transfer of organs and tissues (Transplantation Act)]. URL: http://www.gesetze-im-internet.de/tpg/BJNR263100997.html. (In German).
13. Human Organ Transplants Act, 1989 URL: http:// www.legislation.gov.uk.
14. On ratification of the Association Agreement between Ukraine, on the one hand, and the European Union, the European Atomic Energy Community and their member states, on the other hand: the Law of Ukraine of 16.09.2014. Bulletin of the Verkhovna Rada of Ukraine 2014. - No. 40. - Art. 2021.

15. On the implementation of the Association Agreement between Ukraine, on the one hand, and the European Union, the European Atomic Energy Community and their Member States, on the other hand: the Decree of the Cabinet of Ministers of Ukraine dated October 25, 2017, No. 1106. Cabinet of Ministers of Ukraine. URL: https://zakon.rada.gov.ua/laws/show/1106-2017-%D0%BF#n13.
16. Commission Directive 2004/23 / EU of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, inspection, processing, preservation, storage and distribution of human tissues and cells. Official bulletin, 2004;7(102):48-58.
17. Commission Directive 2006/17 / EU of 8 February 2007 laying down rules for the implementation of Directive 2004/23 / EU of the European Parliament and of the Council on certain technical requirements relating to the donation, procurement and testing of tissues and cells of human origin. Official Journal of the European The union. 2006;9(38):40-52.
18. Commission Directive 2006/86 / EU of 24 October 2006 implementing Directive 2004/23 / EU of the European Parliament and of the Council on the requirements for monitoring, reporting of serious adverse reactions and events, and certain technical requirements for the coding, processing, storage, accumulation and distribution of tissues and cells of human origin. Official Journal of the European Union, 2006:25(294):32-50.
19. International Registry on Organ Donation and Transplantation (IRODaT), June 2018. URL: http://www.irodat.org/img/database/pdf/NEWSLETTER2018_June.pdf

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR
Marina Novytska
Department of Administrative,
Economic Law and Financial and Economic Security
of the Educational and Scientific Institute of Law,
Sumy State University
Petropavlovskaya str., 59, 40000 Sumy, Ukraine
tel: +380505274497
e-mail: marina.novytska@gmail.com

Received: 15.04.2019
Accepted: 18.06.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

IMPLEMENTATION OF THE RIGHT TO HEALTH CARE IN THE COUNTRIES OF THE EUROPEAN UNION

Yuliya Nazarko[1], Oleksandr Iliashko[2], Natalia Kaminska[1]
[1]NATIONAL ACADEMY OF INTERNAL AFFAIRS OF UKRAINE, KYIV, UKRAINE
[2]EDUCATIONAL AND SCIENTIFIC HUMANITARIAN INSTITUTE OF V. I. VERNADSKY TAURIDA NATIONAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Introduction: The right to health is exercised through a complex system of state and social measures of legal, economic, social, scientific, cultural, educational, organizational, technical, sanitary and hygienic nature, aimed at preserving and improving the health of people , lengthening the life expectancy and working capacity, creating good living and working conditions, providing physical and mental development for children and young people, and preventing and managing illnesses and their treatment.

The aim: Investigate the international legal and constitutional legal regulation of the right to health care in the countries of the European Union.

Materials and methods: The article analyzes the Constitution of the European Union, a number of international legal acts and judgments of the European Court of Human Rights.

Review: Each country defines the conditions for realizing the right to health care, according to which people should be healthy, the state itself assumes the obligations of the controller and the protection of this right. These provisions should primarily be enshrined in the Basic Laws - the constitutions. The main direction of state policy in reforming social relations is the achievement of European international legal standards in all spheres of public life. These standards fix the principles, guarantees of norms that determine the scope of human rights, in particular the right to health care.

Conclusions: The main problem of ensuring and realizing the right to health in the European Union, as in many countries, is the financing of this industry, because in general, it is impossible to talk about free medical care in the European Union. There are also problems in the field of investment in health care. The urgent issues of primary health care and public health and the elderly dependence period.

KEY WORDS: the right to health; health care; European Court of Human Rights; Human Rights; public health

Wiad Lek 2019, 72, 7, 1337-1342

INTRODUCTION

Health is a very complex system of state and social measures of legal, economic, social, scientific, cultural, educational, organizational, technical, sanitary and hygienic, aimed at preserving and improving the health of people, extending life expectancy and the creation of good living and working conditions, the provision of physical and mental development for children and young people, as well as the prevention of illness and its treatment.

The right to health is realized through a multitude of other, constitutionally enshrined human rights. This is due to the fact that health care is a system of measures aimed at ensuring the preservation and development of physiological and psychological functions, optimal capacity for work and social activity of man at the maximum biologically possible individual life expectancy.

The effectiveness of international and national law is determined by the real results achieved in the application of its norms. To achieve the desired results, the state adopts various measures of a legal and organizational nature. The right to health is the right of a person, which ensures the state of optimum preservation, development of physiological, psychological functions of the human body.

THE AIM

Investigate the constitutional and normative legal regulation of the right to health care in the countries of the European Union.

MATERIALS AND METHODS

The article analyzes the constitutional and legal regulation of the right to health care in the countries of the European Union, nfrj; we examined and studied the international instruments of these countries, namely the European Social Charter, the Lisbon Treaty and the Constitution of the countries of the European Union. Examined a number of decisions of the European Court of Human Rights in matters related to health care. In the process of research, philosophical methods are used: dialectical, rational, critical; general sciences: analysis, synthesis, systemic, structural-functional, comparative, generalization, historical, as well as special legal methods: formal-legal, methods of interpretation of law, study of legal practice, comparative law.

REVIEW AND DISCUSSION

An important document for the countries of the European Union is the European Social Charter [1], which is equally ratified by Ukraine in 2006. In Art. 11 refers to the "right to health care", namely, to ensure the effective exercise of the right to health care. The parties have undertaken themselves or in cooperation with public or private organizations to respond measures to eliminate, as far as possible, the causes of poor health; to provide activity of

advisory and educational services which would promote health improvement and increase of personal responsibility in health matters; to prevent, as far as possible, epidemic, endemic and other diseases, as well as accidents.

Also Article 13 [1] refers to medical and social assistance, namely: 1. to ensure that any poor person who is unable to obtain sufficient funds by his own efforts or from other sources, in particular through social security assistance, has been provided with appropriate assistance, and in the event of illness, the care provided by his state of health is provided; 2. to ensure that the political or social rights of persons receiving such assistance are not restricted on this basis; 3. to provide that each person may receive in the relevant public or private services such advice and personal assistance as may be necessary to prevent the emergence of a personal or family situation in need, to overcome it or facilitate it.

Consequently this document is fundamental to the definition of the right to health care in the countries of the European Union. It is he who proclaims the effective implementation of the right to health care as well as means for improving health. But there are a number of other documents that proclaim this right for certain segments of the population, in particular women, children, refugees, foreign workers, representatives of national minorities, prisoners, mentally retarded people and people with disabilities, etc.

Article 172 of the Treaty establishing the European Union [2] states that a high level of human health protection should be ensured in the definition and implementation of all activities of the community. At the same time, the EU's actions only complement the national policy of the states in the field of health care. In the European Union, healthcare is the prerogative of national governments and, with a few exceptions, medical care is provided in accordance with the so-called secondary principle, which means that health decisions are taken at the lowest possible level and the EU has still not made a decision on matters of national jurisdiction in the field of health protection or financing of this sphere. This is due to the diversity and differences in the cultural and economic nature of individual social protection systems, rather than the approach of Member States to the importance of social protection and healthcare. By developing health systems, most European countries are trying to adhere to the so-called "international health system standard", which covers: general population servicing through obligatory participation; the integrity of the basic social benefits; contributions based mainly on income, and not on the purchase of individual insurance; cost control through an administrative mechanism (including mandatory service pricelist, global budgets and investment restrictions).

The main direction of state policy in reforming social relations, in particular in Ukraine, is European integration, that is, the achievement of European international legal standards in all spheres of public life. That is why we must adhere to the international legal standards in the field of health care. These standards fix the principles, guarantees of norms that determine the scope of human rights, in particular the right to health care.

International instruments defining human rights play an important role in establishing respect for basic fundamental values. The broad definition of the World Health Organization by the concept of "health" is inaccessible to any society, while it is not considered in the context of the functions and tasks of the state. Therefore, some scholars find it expedient to narrow the concept of health to the realistic capabilities of the systems in which they are, that is, the capabilities of states [3, art. 46].

Consequently, each country determines the conditions for realizing the right to health care, according to which people should be healthy, the state itself assumes the obligations of a catcher and the protection of this right. These provisions should primarily be enshrined in the Basic Laws - the constitutions.

After analyzing the constitutions of the countries of the European Union, we want to draw your attention to the fact that individual countries of the European Union do not have the relevant health standards in their constitutions. But the consolidation of this issue at the constitutional level does not matter to the realization of the right to health care. Interestingly, these countries have nothing in common and adopted their constitution at different times. Thus, countries that have not consolidated the right to health in their constitutions are England [4], Ireland [5], Latvia [6], Malta [7], Cyprus [8], Germany [9], Denmark [10], Sweden [11] and France [12].

Although there is no constitutional right to health protection in these countries, this issue has been resolved in detail by the sectoral legislation of these countries. The issues of compulsory insurance, the range of free services, as well as the place of central and decentralized health care management are carefully capitalized and regulated in each of these states.

The right to health is predominantly enshrined in the constitutions, definitely having different meanings and expressions, but sometimes this right is not enshrined in the constitutions. The majority of constitutions are not defined in the issue of financing health care, that is, the authorities impose the exercise of this right on the citizen himself, namely on health insurance. Close attention is paid to public health, state guarantees and the regulation of free health insurance for certain strata of the population. Free medical care is enshrined in the constitutions of Italy [13], Bulgaria [14], Lithuania [15], Poland [16], Portugal [17].

Interesting in our opinion is the Constitution of Hungary [18] and Portugal [17]. The Constitution of Hungary defines the right to physical and mental health of a person. Hungary has enacted the Constitution on access to healthy food and drinking water, environmental protection, and the provision of systematic physical education. Sanitary education is prescribed as the basis of basic knowledge of citizens about the care of their health. The Portuguese Constitution defines the steps that the state must take to ensure the right to health care. These are areas of financial support for health care, medical services and the produc-

tion of medicines and medical products. It also mentions the responsibility to protect and strengthen the right to health. Consequently, it establishes not only the right, but also the responsibility of individuals for health care.

The Spanish Constitution [19] refers to public health. As this norm reinforces the importance of taking care of the health of the population as a whole, as well as obliges the public authorities to organize public health protection, to take preventive measures, to provide the necessary assistance and services.

The system of decentralized management at a sufficient level in Denmark, they have developed a system of self-governance in this area and a scheme for allocating budgets. Namely about the insurance system is an expedient system of Germany. There is a compulsory and private insurance, and an interesting bonus system, which guarantees the right to health insurance not only for employees but also for those who have lost their job. It also means that the rich can help the poor, but healthy patients. We believe it is also important to devote more attention to the right to a clean environment, as in the French Constitution [12]. Because this is an important part of the right to health. The French Constitution states that the environment is a common heritage for all people.

It has also been determined that different countries use different terms for the right to health (Portugal [17], Poland [16], etc.), the right to health (Hungary [18], Italy [13]), the right to protection health (Czech People's Republic [20], Estonia [21]), right to health care (Lithuania [15]). In our opinion, the most successful and complete definition is the right to health care.

Interestingly, EU members have direct access to medical care in any EU country, with a European Health Insurance Card and identity document.

The state of health of citizens of a certain state determines the level of labor productivity in society, greatly affects the prospects of its socio-economic development. Specialists from the World Health Organization stop by the fact that healthy people can achieve development in all spheres of life.

For example the European Union considers health protection as one of the most important areas of its policy. She tries to help ensure the highest possible level of health of the population. This can be achieved both through active cooperation between the Member States of the Community and by pursuing an appropriate policy at the level of each of the States. The main goal of this policy is the general prevention of diseases, especially severe diseases, drug addiction. The study of the causes of such diseases and the peculiarities of their spread, dissemination of information on the state of health of the population, as well as the upbringing of the young generation of the principles of a healthy lifestyle is being carried out.

The Single European Act provided for cooperation within the Community on health and harmonization of labor protection standards. Only a treaty on the creation of the EU has set up a common health policy. The common health policy has mandated all member countries to coordinate their internal policies and programs and to properly inform the European Commission, which acts as its initiator and coordinator. As the EU as a whole, all member countries support cooperation with third countries and international health organizations, as the health problem is global in nature.

The fundamental differences in the healthcare systems of the European Union have undergone significant changes because of the need to limit health care expenditures. The general question is the problem of financing health care. The main reason for such problems is, firstly, the sharp increase in health care costs due to several factors, such as the rapid development of new cost-effective medical technologies, the high cost of new drugs and the socialization of social problems. Secondly, the decline in economic development, attempts to provide reliable public funding and the desire to reduce production costs, in order to create employment, exert considerable pressure on funding opportunities. And in the end, demographic aging significantly impedes the collective provision of medical care costs [22].

Consequently the main problems of providing, as in many countries, are the financing of this industry, because in general, it is impossible to talk about free medical care in the European Union. Moreover, the insurance institute is the main means for citizens to exercise their right to health care. For in the twentieth century, public protection developed on the basis of two models: the first - compulsory social insurance, and the second - the creation of a system of national health services, which is reduced to minimum services.

There are quite a few cases when patients in the search for decent treatment move to another country. On the contrary, doctors go to help their colleagues from another EU country. The relevant practice has a positive experience, and the participants of the conference reported it. Experts believe that the European Commission should create a forum that will monitor the professional mobility of doctors on the basis of a single data bank. Therefore, the very important factors are the transparency and the desire to share information on professional registration. It was recognized that not all national governments are capable of fully securing capital investment in the health sector, and therefore inevitably have private investment. Private investors have asked the tax and health authorities to formulate and implement their initiatives [22].

"Electronic" healthcare is a tool for providing the appropriate level of information, the choices that are required for European consumers and patients. Today it is not possible to formulate a health policy without taking into account the "electronic" system. Internet medicine is gaining momentum in Ukraine and is an advanced mechanism in the countries of the European Union. It is designed to provide access, continuity to health-related issues. Internet medicine is a collaborative process that enhances and changes the interaction between participants in social security and health systems. But this system should be regulated by the relevant legislation.

It is also necessary to ensure that patients are informed about the emergence of new drugs, their properties and the conditions of their use. In addition, there is an urgent need for greater transparency in the field of clinical trials of medicines and legislative regulation of their implementation. It is also necessary to formulate the concept of innovation and stimulate research on comparative data on medicines and new technologies in the field of health at European level. Again, primary health care and public health should be a priority in the development of health care systems. Yes, it was proposed to create a European Primary Care Forum.

Finally, the onset of the period of medical dependence of elderly people (who not only are consumers of long-term care, but rather support it) should be delayed for as long as possible. This can be achieved through the organization of a public company promoting healthy lifestyles among the elderly [22]. Thus, we considered the general problems in the provision of human rights to health.

The text of the European Convention on Human Rights does not contain a separate article defining the human right to health, but let's consider how then the European Court of Human Rights resolves the issue of violating the right to health care.

Let's begin with access to experimental treatment or a remedy in the case of Hristosov and others v. Bulgaria [23]. Ten applicants who had cancer were complaining that they were denied access to unauthorized experimental cancer therapies. In accordance with the law of Bulgaria, such a permit can be issued only if the medicine has been authorized in another country. While medications were allowed for "philanthropic use" in some countries, they were officially not allowed. Accordingly, the authorities of Bulgaria refused to issue a permit.

The European Court of Human Rights ruled that Article 8 (right to respect for private and family life) of the European Convention on Human Rights had not been violated. Given the limitation of the patient's right to respect for private life, as provided for in Article 8 of the Convention, the tendency was to provide the possibility, in exceptional circumstances, of the use of unauthorized medicine in European countries. However, the court acknowledged that this consensus was based not on the consistent principles of the legislation of these countries and did not extend to the precise order governing the use of such drugs. The Court also held that Article 2 (right to life) and article 3 (prohibition of torture and inhuman or degrading treatment) of the Convention were not infringed in this case.

In addition the right to medical information is the case of K. H. and others v. Slovakia [9]. The applicants, eight women of Roman origin, could no longer become pregnant after being treated at a gynecological department in two different hospitals and suspected of having been sterilized while staying in these hospitals. They complained that they could not get a copy of their disease history. The Court ruled that Article 8 (right to respect for private and family life) of the Convention was infringed by the fact that the applicants were not able to make photocopies of their medical records.

There are interesting cases of organ transplants. The case of Petrova v. Latvia [14], from the case file, having received life-threatening injuries during an automobile accident, the applicant's son was taken to a hospital where he died. Thereafter, laparotomy was carried out on his body, during which his kidneys and spleen were removed for the purpose of transplantation of organs. The applicant alleged that the removal of her son's organs was carried out without her consent or with the prior consent of her son, and that, in any case, no attempt was made to substantiate her opinion.

The court ruled that there had been a violation of Article 8 (right to respect for private and family life) of the Convention. It was established that the law of Latvia on organ transplantation at the time of the death of the applicant's son was insufficiently clear, which led to the emergence of circumstances in which the applicant, as the closest relative of her son, had certain rights regarding the removal of his organs, but was not informed - not to mention any explanation of how and when these rights could be used.

Case Elberte v. Latvia [15] concerned the removal of body tissue from an applicant's deceased husband by medical experts after his death without her knowledge. Without the consent of the applicant, an agreement approved by the state, the fabric was removed from the body of the man after it was opened and sent to a pharmaceutical company in Germany for the creation of bio-implants. She learned about the course of events two years after her husband's death, when a criminal investigation was launched in Latvia in connection with allegations of large-scale illegal extraction of organs and tissues from the dead. However, the local authorities did not establish any form of crime.

The applicant complained, in particular, that the removal of her husband's organs was carried out without her prior consent. She also complained about emotional suffering, when she remained in a state of uncertainty as to the circumstance of removing the tissue from the body of her husband, her husband's body was returned to her after having been crucified with her legs.

The Court held that there had been a violation of Article 8 (right to respect for private and family life) and violation of Article 3 (Inhuman or Degrading Treatment) Convention. It has been established, in particular, that the Latvian law on the functioning of the requirements for obtaining consent for tissue removal is lacking in clarity and does not have sufficient legal safeguards against arbitrariness, although it establishes the legal framework that allows the closest relatives to consent or refuse to remove tissues, this law is not defines clearly the respective responsibilities or discretion of the experts for obtaining an agreement. Indeed, the way used to apply the rights of relatives to express their wishes and the extent of the responsibilities for obtaining consent was the subject of disagreement in the national authorities. The Court further found that the applicant had experienced a long period of uncertainty and suffering in relation to the origin, method and purpose of removing the tissue from her husband's body, noting that, in the field of organ transplantation, the human body should be respected even after death.

Case J.N. and others v. Italy [12] concerned the infection of the applicants or their relatives with the AIDS or

hepatitis C. The interested parties suffered from hereditary disorders (thalassemia) and were infected during blood transfusion, conducted by the State Health Service. The applicants complained, in particular, that the authorities did not carry out the necessary screening to prevent infection. They also complained about shortcomings in the subsequent civil proceedings and the refusal to pay them compensation. In addition, they claimed to have been discriminated against in other groups of infected individuals.

The Court held that Article 2 (right to life) of the Convention had not been violated in relation to the protection of life of applicants and their relatives, taking into account, that it had not been established that at the time of the proceedings the Ministry of Health was aware or one should be aware of the risk of transmission of ACID or hepatitis through blood transfusions, and it was impossible to determine from what moment the Ministry knew or should have been aware of the risk. The Court also held that there had been a violation of Article 2 of the Convention in respect of civil proceedings, given that the Italian judiciary, when considering disputed complaints under Article 2, was not able to provide an appropriate and prompt response in accordance with the procedural obligations of the State in accordance with the ruling. It has been found that there has been a violation of Article 14 (prohibition of discrimination), in conjunction with Article 2 of the Convention, by establishing that applicants, patients with thalassemia or their heirs were discriminated against in comparison with hemophiliac patients who had the opportunity to use the extrajudicial decision of the case proposed by the Ministry.

After analyzing a number of cases of the European Court of Human Rights, it may be concluded that although the text of the European Convention on Human Rights does not contain a separate article defining the human right to health, but the practice of the European Court of Human Rights in matters of the field Healthcare suggests that rights in this area can be protected by referring to a violation of Article 3 of the Convention if the process and results of failure to provide or inadequate medical assistance were in fact capable of being treated as torture or inhuman or degrading treatment. In some cases, there may also be a violation of Article 8 of the Convention, namely the right to respect for private and family life or article 14 on the prohibition of discrimination. In the case of the consequences of failure or inadequate provision of medical care are more substantial, reference should be made to the violation of Article 2 - if the death of the person ended.

It is very important to study in more detail the practice of the European Court of Human Rights to understand the logic and case-law of the Court with regard to "medical matters". It is very important for courts to take into account, when making a decision, the extent of the consequences of the actions or inaction of the defendants; analyze the findings of the forensic examination and expert testimonies within the framework of the trial from the standpoint of its objectivity and substantiation of the findings, as well as compliance with the actual circumstances of the case.

CONCLUSIONS

So in order to fully investigate the constitutional and legal regulation of the right to health in the countries of the European Union, we examined and studied the international instruments of these countries, namely the European Social Charter, the Lisbon Treaty and the Constitution of the countries of the European Union. They also appealed to the practice of decisions of the European Court of Human Rights in matters related to health care. They have determined that the main problem of ensuring and implementing the right to health in the European Union, as in many countries, is the financing of this industry, because in general, it is impossible to talk about free medical care in the European Union.

Moreover, the insurance institute is the main means for citizens to exercise their right to health care. Those primary health care and public health issues should be a priority in the development of health systems in the European Union. There are also problems in the field of investment in health care. Turned to tools such as "electronic" healthcare - an instrument for providing the appropriate level of information; Awareness of patients about the emergence of new drugs. Again, they dwelt on issues of primary health care and public health, which should be a priority in the development of health systems. Finally, talked about the dependency period of the elderly (who not only are consumers of long-term care, but rather support it) should be delayed for as long as possible.

REFERENCES

1. European Social Charter: Charter of the Council of Europe of 3 May 1996.Retrieved from http://zakon0.rada.gov.ua/laws/show/994_062 (Accessed 06 May 2019).
2. Treaty establishing the European Community: EU Treaty of 17.02.1986. Retrieved from http://zakon2.rada.gov.ua/laws/show/ru/994_017 (Accessed 06 May 2019) .
3. Gostin L.O., Lazzarini Z. Human Rights and Public Health in the AIDS Pandemic. New York: Oxford University Press, 1997. 232 p.
4. The Great Charter of the Liberty of England: the Charter of 1215. Retrieved fromhttps://www.constituteproject.org/constitution/United_Kingdom_2013?lang=en (Accessed 06 May 2019) .
5. The Constitution of Ireland of July 1, 1937. Retrieved from http://www.irishstatutebook.ie/eli/cons/en/html (Accessed 06 May 2019) .
6. The Constitution of Latvia of February 15, 1922. Retrieved from http://www.saeima.lv/en/legislation/constitution (Accessed 06 May 2019).
7. The Constitution of Malta of August 1974. Retrieved from http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8566 (Accessed 06 May 2019) .
8. The Constitution of Cyprus of 14 July 1960. Retrieved from http://www.partylaw.leidenuniv.nl/party-law/4c8b8962-6c8c-43fb-8c95-19057287acdc.pdf (Accessed 06 May 2019) .
9. The Constitution of Germany of August 11, 1919. Retrieved from https://www.btg-bestellservice.de/pdf/80201000.pdf(Accessed 06 May 2019).
10. The Constitution of Denmark from 1953. Retrieved from https://www.constituteproject.org/constitution/Denmark_1953.pdf(Accessed 06 May 2019).
11. Constitution of Sweden from 1974. Retrieved from http://www.parliament.am/library/sahmanadrutyunner/Sweden.pdf (Accessed 06 May 2019).

12. French Constitution of October 04, 1958. Retrieved from http://www.conseilconstitutionnel.fr/conseilconstitutionnel/english/constitution/constitution-of4-october-1958.25742.html (Accessed 06 May 2019).
13. The Italian Constitution of December 22, 1933. Retrieved from https://www.senato.it/documenti/repository/istituzione/costituzione_inglese.pdf (Accessed 06 May 2019) .
14. The Constitution of Bulgaria of 13 July 1991. Retrieved from http://www.parliament.bg/en/const (Accessed 06 May 2019).
15. The Constitution of Lithuania of October 25, 1992. Retrieved from http://www3.lrs.lt/home/Konstitucija/Constitution.htm (Accessed 06 May 2019).
16. Constitution of the Republic of Poland of 2 April 1997. Retrieved from http://www.sejm.gov.pl/prawo/konst/angielski/kon1.htm(Accessed 06 May 2019) .
17. The Portuguese Constitution of 1976. Retrieved from https://www.constituteproject.org/constitution/Portugal_2005.pdf (Accessed 06 May 2019) .
18. Hungarian Constitution of 18 April 2011. Retrieved from https://www.constituteproject.org/constitution/Hungary_2011.pdf (Accessed 06 May 2019).
19. Spanish Constitution of 31 October 1978. Retrieved from http://www.congreso.es/portal/page/portal/Congreso/Congreso/Hist_Normas/Norm/const_espa_texto_ingles_0.pdf (Accessed 06 May 2019).
20. Charter of Fundamental Rights and Freedoms of the Czech Republic dated December 16, 1992. Retrieved from http://www.psp.cz/en/docs/laws/constitution.html (Accessed 06 May 2019).
21. The Constitution of Estonia of June 28, 1992. Retrieved from https://www.president.ee/en/republic-of-estonia/the-constitution (Accessed 06 May 2019) .
22. Information publication of the Delegation of the European Commission to Ukraine: European Commission, 2005. Retrieved from http://parlament.org.ua/wpcontent/uploads/2016/10/evrobulet_06.pdf(Accessed 06 May 2019) .
23. Case Hristozov and Others v. Bulgaria: judgment of European Court of Human Rights 13 november 2012. Retrieved from https://hudoc.echr.coe.int/eng#{«itemid»:[«002-7298»]} (Accessed 06 May 2019).
24. Case K.H. and Others v. Slovakia: judgment of European Court of Human Rights 28 april 2008. Retrieved from https://www.escr-net.org/caselaw/2009/kh-and-others-v-slovakia-european-court-human-rights-application-no-3288104(Accessed 06 May 2019) .
25. Case Elberte v. Latvia: judgment of European Court of Human Rights 27 april2010.Retrievedfromhttps://hudoc.echr.coe.int/app/conversion/pdf/?library=ECHR&id=001-111489&filename=001111489.pdf&TID=zcgcorwhax(Accessed 06 May 2019) .
26. Case Petrova v. Latvia: judgment of European Court of Human Rights 24 september 2014. Retrieved from https://hudoc.echr.coe.int/app/conversion/pdf/library=ECHR&id=0029531&filename=002(Accessed 06 May 2019) .
27. Case G. N. and others v. Italy: judgment of European Court of Human Rights december 2009. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20443445(Accessed 06 May 2019) .

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Yuliya Nazarko
National Academy of Internal Affairs of Ukraine
Kyiv, Ukraine
tel: +380675060760
e-mail: deliko@email.ua

Received: 22.02.2019
Accepted: 03.06.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

TELEKONSULTACJE LEKARSKIE W POLSKIM SYSTEMIE OCHRONY ZDROWIA

MEDICAL TELECONSULTATION IN THE POLISH HEALTHCARE SYSTEM

Małgorzata Paszkowska
WYŻSZA SZKOŁA INFORMATYKI I ZARZĄDZANIA W RZESZOWIE, RZESZÓW, POLSKA

STRESZCZENIE

Telemedycyna jest to stosunkowo nowa forma medycyny i opieki zdrowotnej łącząca w sobie elementy telekomunikacji, informatyki oraz medycyny. Telemedycyna ma coraz większe znaczenie także w Polsce. Obecnie prawo pozwala na udzielanie świadczeń zdrowotnych lekarskich z wykorzystaniem systemów teleinformatycznych. Dla lekarzy w praktyce największe znaczenie ma możliwość udzielania telekonsultacji medycznych. Płatnik publiczny(Narodowy Fundusz Zdrowia) finansuje w Polsce telekonsylium kardiologiczne oraz geriatryczne jako specyficzne odrębnie kontraktowane kategorie świadczeń gwarantowanych. Przedmiotem artykułu jest przedstawienie możliwości udzielania telekonsultacji lekarskich w polskim systemie ochrony zdrowia.

SŁOWA KLUCZOWE: opieka medyczna, telemedycyna, odległość, świadczenia gwarantowane, prawo

ABSTRACT

Telemedicine is a relatively new form of medicine and healthcare combining elements of telecommunications, IT and medicine. Telemedicine is also increasingly important in Poland. Currently, the law allows for the provision of medical health services using ICT systems. For physicians in practice the most important is the possibility of teleconsultation. The public payer (National Health Fund) is financing in Poland the teleconsylum cardiology and geriatrics. The subject of the article is the presentation of the possibility of providing medical teleconsultations in the Polish healthcare system.

KEY WORDS: health care, telemedicine, distance, guaranteed services, law

Wiad Lek 2019, 72, 7, 1343-1349

WSTĘP

Rozwój technologii informatycznych i telekomunikacyjnych spowodował powstanie nowej formy medycyny/opieki zdrowotnej, tj. medycyny na odległość tzw. telemedycyny. Telemedycyna jest to stosunkowo nowa forma opieki zdrowotnej łącząca w sobie elementy telekomunikacji, informatyki oraz medycyny. Od lat rozwija się w Stanach Zjednoczonych, Australii, a także w Skandynawii. Także w polskim systemie ochrony zdrowia zaczyna mieć powoli coraz większe znaczenie, czemu sprzyjają w ostatnich latach zmiana prawa oraz wprowadzenie świadczeń telemedycznych do katalogu świadczeń gwarantowanych. Telemedycyna występuje w różnych zakresach, z czego dla lekarzy podstawowe znaczenie ma możliwość udzielania tzw. telekonsultacji lekarskich. Ponadto istotna i wykorzystywana w praktyce jest także teleedukacja (nauczanie na odległość).

Głównym celem niniejszego artykułu jest przedstawienie możliwości udzielania telekonsultacji lekarskich w polskim systemie ochrony zdrowia. Celem szczegółowym artykułu jest odpowiedź na dwa podstawowe pytania: po pierwsze, czy lekarz w Polsce może w świetle prawa legalnie udzielać konsultacji telemedycznych oraz czy telekonsultacje lekarskie są świadczeniami gwarantowanymi w systemie publicznego ubezpieczenia zdrowotnego?

W niniejszej pracy dokonano przede wszystkim analizy aktualnie obowiązujących norm prawnych w zakresie telemedycyny i zasad wykonywnia zawodu lekarza. Ponadto dokonano analizy adekwatnych do tematu norm prawnych dotyczących świadczeń zdrowotnych gwarantowanych oraz związanego z nim piśmiennictwa. W pracy zastosowano metodę analityczno-syntetyczną, a także wykorzystano dane Narodowego Funduszu Zdrowia.

POJĘCIE I ROZWÓJ TELEMEDYCYNY

Słowo „telemedycyna" pochodzi od greckiego słowa *tele* (na odległość) i łacińskiego *mederi* (leczenie). Istnieje wiele definicji telemedycyny, jedna z prostszych i adekwatniejszych zdaniem autorki definicji stanowi, że jest to praktyka

lekarska oraz edukacja medyczna odbywająca się za pośrednictwem interaktywnej komunikacji wykorzystującej teleinformatyczne urządzenia przesyłające dźwięk i obraz, a nie poprzez bezpośrednią fizyczną interakcję lekarz – pacjent[1]. Inna, bardziej ogólna, uznawana przez zajmujące się tą tematyką czasopismo „Journal of Telemedicine and Telecare", określa telemedycynę jako działalność medyczną na odległość, z podkreśleniem istotności edukacji medycznej oprócz samego procesu diagnozy i leczenia [2]. Natomiast Amerykańskie Stowarzyszenie Telemedycyny ATA (*American Telemedicine Association*) definiuje, że telemedycyna jest formą wymiany informacji medycznych pomiędzy dwiema stronami, przebiegającą przy wykorzystaniu narzędzi telekomunikacyjnych, której celem jest poprawa stanu zdrowia pacjenta [3]. Według dokumentu z 1998 roku, *Information for Health: An information strategy for the modern NHS*, telemedycyna obejmuje aktywności związane z ochroną zdrowia (w tym diagnostykę, porady, leczenie i monitorowanie), w których uczestniczy pracownik opieki zdrowotnej i pacjent lub dwóch pracowników ochrony zdrowia, oddzielonych od siebie w przestrzeni, a niekiedy także w czasie. Bardziej kompleksowo w polskim piśmiennictwie zdefiniowano, iż telemedycyna to transfer informacji medycznych z jednego odległego miejsca do innego, który wykorzystuje elektroniczną komunikację w celu prewencji chorób, utrzymania zdrowia, zapewnienia opieki zdrowotnej pacjenta i jej monitoringu, edukacji pacjentów i osób świadczących im opiekę zdrowotną, a także wparcia pracowników opieki zdrowotnej z innych dyscyplin. To zdalna medyczna diagnoza, konsultacja i leczenie, które można zastosować synchronicznie (w czasie rzeczywistym) lub asynchronicznie [4]. Pojęcie telemedycyny bezspornie obejmuje także zdalne prowadzenie szkoleń personelu medycznego, konferencji czy też procedur diagnostycznych i leczniczych.

Mimo prób zdefiniowania telemedycyny w polskim prawie, ustawodawstwo polskie nie zawiera obecnie żadnej definicji telemedycyny. Termin „telemedycyna" został użyty w ustawie o systemie informacji w ochronie zdrowia, w artykule 36, który odnosił się do portalu edukacyjno-informacyjnego, utworzonego i prowadzącego przez ministra właściwego do spraw zdrowia. Jednym z celów portalu określonym w art. 36 ust.1 pkt 4 było„ upowszechnianie wiedzy na temat funkcjonowania systemów informatycznych w ochronie zdrowia oraz telemedycyny". Artykuł 36 ustawy o systemie informacji w ochronie zdrowia obecnie nie obowiązuje, bowiem został uchylony(z dniem 23 sierpnia 2018).

Telemedycyna jest w krajach wysoko rozwiniętych ważnym uzupełnieniem bezpośredniego kontaktu lekarz – pacjent. Forma ta przynosi szereg korzyści, m.in. przyspiesza diagnostykę, ułatwia dostęp do opieki zdrowotnej osobom oddalonym od ośrodków medycznych, ogranicza koszty związane m.in. z transportem. Zastosowanie narzędzi telemedycznych przyczynia się do usprawnienia diagnozy w przypadku, gdy dostęp do specjalisty w danej dziedzinie jest utrudniony, ponadto jest jedną z mniej kosztownych oraz znacznie bardziej oszczędnych czasowo metod monitorowania pacjentów i prewencji np. w kardiologii, jak również bardzo dobrze nadaje się do archiwizacji i przepływu danych medycznych.

Podstawowym narzędziem wykonywania usług medycznych na odległość pozostaje internet. Internet (łac. *inter* między, ang. *net* sieć, dosłownie *międzysieć*) to ogólnoświatowa sieć komputerowa logicznie połączona w jednorodną sieć adresową opartą na protokole IP. Dostarcza lub wykorzystuje usługi wyższego poziomu oparte na telekomunikacji i związanej z nią infrastrukturze. Internet w drugiej dekadzie XXI wieku stanowi powszechne już medium przekazu informacji oraz komunikowania się między ludźmi. Umożliwia komunikację dwukierunkową i ma globalny zasięg(geograficznie i czasowo – 24 godziny na dobę).

Kolebką współczesnej telemedycyny są Stany Zjednoczone. W drugiej połowie XX wieku, właśnie tam nastąpił rozwój tej dziedziny. Wpływ na to miały przygotowania do lotu w kosmos przez NASA (Narodowa Agencja Aeronautyki i Przestrzeni Kosmicznej Stanach Zjednoczonych). Na potrzeby bezpieczeństwa podróży w kosmos NASA stworzyła zabezpieczenia w postaci zbioru wiedzy i narzędzi do zdalnego, stałego monitorowania parametrów życiowych człowieka. W rezultacie możliwe było zdalne pomiary tętna, ciśnienie krwi oraz EKG. Dorobek techniczny NASA z lat 50.–60. XX wieku, z czasem został wdrożony do użytku powszechnego [5]. Telemedycynę w Europie zapoczątkował Związek Radziecki, który stworzył system do zdalnego monitorowania tętna organizmu (tętna psa „Łajki" wystrzelonej w satelicie w przestrzeń kosmiczną w 1957 roku). Milowy krok w rozwoju telemedycyny nastąpił 7 września 2001 roku, kiedy doszło do wykonania pierwszej operacji chirurgicznej na odległość. Operacja polegała na usunięciu woreczka żółciowego przez lekarza stacjonującego w Nowym Jorku u pacjenta przebywającego w Strasburgu. Projekt ten nosił nazwę „Operacja Lindbergh" [6].

Bezspornie na przełomie lat 80. i 90. XX wieku rozwój telemedycyny uległ znacznemu przyspieszeniu dzięki rozwojowi sieci komputerowych i internetu. Zaczęto gromadzić coraz więcej danych, powstawały coraz lepsze systemy do przesyłania informacji tekstowych, głosowych i obrazowych. Pojawiła się potrzeba zmiany i optymalizacji systemów w celu zwiększenia swobodnej wymiany danych. Wprowadzono standard DICOM (*Digital Imaging and Communications in Medicine Standard*), który ustanowiony został przez kilka amerykańskich instytucji zajmujących się obrazowaniem medycznym oraz przesyłaniem informacji. Ten standard określa ujednolicony sposób i format pobierania, przechowywania i wysyłania informacji medycznych [7].

W Polsce telemedycyna zaczęła się rozwijać zasadniczo dopiero w latach 90. XX wieku. Pierwsze udane inicjatywy w powyższej sferze to m.in. wprowadzanie dla pacjentów w Warszawie i Rzeszowie usługi w zakresie monitorowania pracy serca na odległość tzw. teleekg. Ponadto coraz popularniejsze stawało się uczestnictwo w operacjach i szkoleniach w formie video konferencji. Jednym z pionierów współczesnej telemedycyny w Polsce wraz ze

swoim zespołem jest prof. Henryk Skarżyński. Prowadzi działalność w tej dziedzinie medycyny od początku XXI wieku. Pierwsze telekonsultacje przeprowadzone zostały w 2000 roku. Wtedy to obraz ucha zarejestrowany wideo-otoskopem przesyłany był za pomocą internetu do analizy i konsultacji. To wydarzenie, zapoczątkowało dalsze działania Instytutu oraz promocję telemedycyny w Polsce. Rok 2009 to początki pierwszej w świecie Krajowej Sieci Teleaudiologii.

W 2001 roku została założona Sekcja Telemedycyny Polskiego Towarzystwa Lekarskiego[8]. Głównym celem Sekcji Telemedycyny Polskiego Towarzystwa Lekarskiego jest, krzewienie i rozwój telemedycyny w Polsce. Działania Sekcji koncentrują się na propagowaniu idei i praktycznych zastosowań telemedycyny w środowisku lekarskim, jak również wśród pacjentów, informują o wszelkich nowościach związanych z telemedycyną, medycznych i technologicznych. Organizują również seminaria oraz pokazy poświęcone możliwościom telemedycyny np.: telekonsulacje, interaktywne wideotransmisje z operacji chirurgicznych lub zabiegów gastroskopowych.

Ponadto powstało Stowarzyszenie o nazwie Polskie Towarzystwo Telemedycyny i e-Zdrowia, którego celami są m.in. działalność naukowo-badawcza służąca wspieraniu rozwoju telemedycyny i medycznej rzeczywistości wirtualnej w pracy klinicznej i naukowej na terytorium RP, wspieranie badań naukowych służących rozwojowi telemedycyny i jej zastosowań wspieranie komunikacji telemedycznej pomiędzy ośrodkami medycznymi w kraju oraz ich współpracy z ośrodkami zagranicznymi konsultacje merytoryczne, jak też wspieranie działalności lekarzy, a zwłaszcza lekarzy rodzinnych w małych ośrodkach, przez wskazanie możliwości telediagnostyki i teleedukacji, opiniowanie projektów telemedycznych, działalność edukacyjna propagująca zastosowania telemedycyny i medycznej rzeczywistości wirtualnej wśród lekarzy i innych pracowników służby zdrowia oraz utrzymywanie serwera WWW o tematyce telemedycznej [9].

Obecnie najbardziej rozwija się i upowszechnia telekardiologia, teleradiologia i telerehabilitacja. W systemie publicznego ubezpieczenia zdrowotnego wprowadzono jako pierwsze telemedyczne świadczenia gwarantowane finansowane przez Narodowy Fundusz Zdrowia telekonsultację (telekonsylium) kardiologiczną i geriatryczną (po raz pierwszy Zarządzeniem Nr 63/2015/DSOZ Prezesa Narodowego Funduszu). Obecny rozwój telemedycyny w Polsce związany jest m.in. z deficytem kadr medycznych, a przede wszystkim brakiem lekarzy określonych specjalności, np. geriatrów. Chociaż w Polsce istnieje już wiele programów telemedycznych, są one w zdecydowanej większości regionalne lub lokalne. Nie istnieje spójny program rozwoju tej dziedziny medycyny w skali kraju.

Wzrost znaczenie telemedycyny w Polsce spowodował również podjęcie działań przez samorząd zawodowy lekarzy oraz, co szczególnie ważne wydanie uchwały nr 25/18/P-VIII Prezydium Naczelnej Rady Lekarskiej z dnia 29 czerwca 2018 r. w sprawie powołania zespołu roboczego ds. telemedycyny.

Powszechnie do usług telemedycznych zalicza się: telekonsultacje, teleopiekę, telediagnostykę, telenauczanie oraz telezabiegi. Dla lekarzy w praktyce podstawowe znaczenie w zakresie udzielania usług telemedycznych mają telekonsultacje i telediagnostyka.

Telekonsultacja jest to możliwość przekazania informacji w czasie rzeczywistym i przeprowadzenia konsultacji za pomocą łączy fonii i obrazu, np.: z dziedziny kardiologii, dermatologii, badania ultrasonograficznego itp. lub uzyskania w rozmowie on-line konsultacji medycznej po przedstawieniu problemu, od lekarza specjalisty-konsultanta. Telekonsulatcja polega generalnie na użyciu technologii audiowideo i transmisji on-line. Dzięki temu lekarz konsultujący jest w stanie przeprowadzić wywiad z chorym, a nawet dokonać badania. Zaletą takiego rozwiązania, jest możliwość skonsultowania pacjenta przez konsylium lekarskie, składające się z lekarzy różnych specjalności, co pozwala na wszechstronne spojrzenie na dolegliwości pacjenta [10]. Natomiast telediagnostyka to opis badania, diagnoza, dokonywane na podstawie medycznych danych mulimedialnych (cyfrowych, tekstowych, obrazowych, dźwiękowych), które przesłane są za pomocą sieci telekomunikacyjnych – telefon, czy teleinformatycznych – internet jako zapisane pliki danych. Najczęściej takie opisy wykonywane są w wyspecjalizowanych centrach diagnostycznych. Istnieje wiele odmian telediagnostyki, a do najbardziej rozpowszechnionych możemy zaliczyć: teleradiologię, teleendoskopię, teleUSG, teleEKG[11].

Obecnie w Polsce w praktyce wykorzystywane są w większym lub mniejszym stopniu niektóre rozwiązania telemedyczne, a za wiodące należy uznać rozwiązania w zakresie telekardiologii oraz teleradiologii. Telekardiologia jest najczęściej wykorzystywaną i najbardziej rozwijaną dziedziną zdalnego leczenia pacjentów w Polsce. Obejmuje w szczególności: profilaktykę, diagnostykę, rehabilitację, monitorowanie 24 h, konsultacje i nauczanie. Szacuje się, że około 10% polskich kardiologów wykorzystuje rozwiązania telemedyczne[12]. Jedną z coraz powszechniejszych usług opieki medycznej, a zarazem rozwiązaniem w obszarze telekardiologii jest całodobowa opieka kardiologiczna(zdalny monitoring) oferowana m.in. przez firmę Telemedycyna Polska z siedzibą w Katowicach. Jest to zestaw usług skierowany zarówno dla pacjentów indywidualnych, jak i grupowych dostawców rozwiązań. Monitoring zdalny pozwala na szybką ocenę serca pacjenta poprzez dostęp do danych medycznych przesyłanych zdalnie, na przykład za pomocą aparatu EKG. Telemonitoring kardiologiczny umożliwia wykrywanie nieprawidłowości kardiologicznych i monitorowanie stanu zdrowia osób cierpiących na choroby serca oraz stały kontakt z lekarzem [13].

W praktyce polskiego systemu ochrony zdrowia coraz powszechniej funkcjonuje też teleradiologia. Polega ona zazwyczaj na przesyłaniu przy użyciu systemów IT z jednego podmiotu leczniczego, np. szpitala badań diagnostyki obrazowej, np. MRI, TK celem ich opisania w innym(oddalonym geograficznie) specjalistycznym ośrodku. W rezultacie dochodzi do outsourcingu usługi

(pracowni diagnostycznej). Powstają centra opisów badań np. w Poznaniu prowadzone przez *Hospital Investment Group*. Zespół radiologów opisuje badania RTG, TK, MR i mammografii. Dzięki zaawansowanej technologii badania przydzielane są do opisu według specjalizacji [14]. System teleradiologii generalnie pozwala na szybkie uzyskanie dobrej jakości opisów radiologicznych oraz obniżenie kosztów funkcjonowania pracowni diagnostyki obrazowej. Ponadto centra teleradiologii oferują możliwość konsultacji opisów badań przez specjalistów z różnych ośrodków, a także archiwizację danych z dostępem 24 h. Teleradiologia to prężnie rozwijający się i przyszłościowy rynek pracy dla lekarzy radiologów.

Na rynku pojawia się też coraz więcej ofert systemów teleopieki (niektóre wdrażane są pilotażowo przez samorządy terytorialne). Teleopieka jest usługą, która pozwala ludziom, zwłaszcza starszym lub niepełnosprawnym na bezpieczniejsze prowadzenie samodzielnego życia we własnym domu. Niektóre systemy teleopieki poza opaskami monitorującymi oferują także możliwość korzystania z internetowych konsultacji medycznych w ramach usługi telemedycyny. Przykładowo w ramach usługi systemu opiekuńczo-ratunkowego SilverCRS podopieczny może korzystać z opaski monitorującej: rytm serca, temperaturę, obecność, ruch, upadek, posiadającej przycisk SOS i lokalizację GPS[15].

Należy podkreślić, że projekty związane z telemedycyną i teleopieką otrzymują silne wsparcie ze strony funduszy europejskich w ramach Regionalnych Programów Operacyjnych. Przykładowo w ramach Regionalnego Programu Operacyjnego Województwa Śląskiego na lata 2014-2020 Telemedycyna Polska S.A. realizuje projekt dofinansowany z Funduszy Europejskich Wprowadzenie usługi telemedycznej do zastosowania w profilaktyce, diagnostyce i terapii medycznej w kardiologii opartej o innowacyjne rozwiązania technologiczne oraz organizacyjne przez Spółkę Telemedycyna Polska S.A. Dofinansowanie projektu z UE wyniosło 285 000,00 zł.

PODSTAWY PRAWNE TELEKONSULTACJI LEKARSKICH

Telemedycyna przez wiele lat nie była uregulowana prawem, mimo iż funkcjonowała w praktyce. Wskutek nowelizacji przepisów ustawowych w 2015 roku (Ustawa o zmianie ustawy o systemie informacji w ochronie zdrowia oraz niektórych innych ustaw z 9 października 2015 r. Dz. U. z 2015 r., poz. 1991) obecnie istnieją już regulacje prawne w zakresie telemedycyny w szczególności umożliwiające lekarzom udzielanie świadczeń zdrowotnych na „odległość". Zamiany polskiego prawa w zakresie e-zdrowia związane są m.in. z wdrożeniem prawa unijnego. W prawie polskim nie ma definicji telemedycyny. Pomimo braku definicji ustawowej, uznać należy, iż ustawodawca posługując się terminami „systemy teleinformatyczne" oraz „inne systemy łączności", odnosi się do form komunikacji na odległość, niewymagających osobistego kontaktu między m.in. personelem medycznym a pacjentem.

Kwestia udzielania świadczeń zdrowotnych czy też wykonywania zawodu medycznego „na odległość", a w szczególności udzielanie telekonsultacji przez wiele lat nie była uregulowana prawem. Po nowelizacji przepisów w roku 2015 stan prawny uległ istotnym zmianom [16]. Opieka zdrowotna/usługi medyczne to w nomenklaturze prawnej działalność lecznicza. Wykonywać ją mogą tylko tzw. podmioty wykonujące działalność leczniczą(czyli podmioty lecznicze i praktyki zawodowe lekarzy, pielęgniarek, położnych). Działalność lecznicza w Polsce może być w aktualnym stanie prawnym prowadzona także na odległość. W świetle art. 3 ust.1 ustawy z dnia 15 kwietnia 2011 roku o działalności leczniczej (t. jedn. Dz.U. 2018; poz.160) działalność lecznicza polega na udzielaniu świadczeń zdrowotnych. Po nowelizacji ustawy o działalności leczniczej **świadczenia powyższe mogą być udzielane także za pośrednictwem systemów teleinformatycznych lub systemów łączności.** Działalność lecznicza może również polegać na:

1. promocji zdrowia lub
2. realizacji zadań dydaktycznych i badawczych w powiązaniu z udzielaniem świadczeń zdrowotnych i promocją zdrowia, w tym wdrażaniem nowych technologii medycznych oraz metod leczenia. Czynności wskazane powyżej w pkt 1 i 2 mogą być wykonywane także za pośrednictwem systemów teleinformatycznych lub systemów łączności.

W świetle art.2 pkt 3 ustawy z dnia 18 lipca 2002 r. o świadczeniu usług drogą elektroniczną (Dz. U. 2017; poz. 1219), do której odsyła m.in. ustawa z 28 kwietnia 2011 o systemie informacji w ochronie zdrowia(Dz.U. 2017; poz.1845) system teleinformatyczny to zespół współpracujących ze sobą urządzeń informatycznych i oprogramowania, zapewniający przetwarzanie i przechowywanie, a także wysyłanie i odbieranie danych poprzez sieci telekomunikacyjne za pomocą właściwego dla danego rodzaju sieci telekomunikacyjnego urządzenia końcowego w rozumieniu ustawy z dnia 16 lipca 2004 r. - Prawo telekomunikacyjne (Dz. U. 2016; poz. 1489, z późn. zm.). Telekomunikacyjne urządzenie końcowe to urządzenie telekomunikacyjne przeznaczone do podłączenia bezpośrednio lub pośrednio do zakończeń sieci. Natomiast dziedzinowy system teleinformatyczny to zgodnie z ustawą o systemie informacji w ochronie zdrowia system teleinformatyczny wspomagający określony obszar funkcjonowania systemu ochrony zdrowia.

Obecnie, zgodnie z obowiązującym prawem, lekarz może wykonywać czynności wchodzące w zakres wykonywania zawodu lekarza także „telemedycznie"/na odległość. W świetle art. 2 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty(t. jedn. Dz.U. 2019; poz.537) wykonywanie zawodu lekarza polega na udzielaniu przez osobę posiadającą wymagane kwalifikacje, potwierdzone odpowiednimi dokumentami, świadczeń zdrowotnych, w szczególności: badaniu stanu zdrowia, rozpoznawaniu chorób i zapobieganiu im, leczeniu i rehabilitacji chorych, udzielaniu porad lekarskich, a także wydawaniu opinii i orzeczeń lekarskich. Natomiast wykonywanie zawodu

lekarza dentysty polega na udzielaniu przez osobę posiadającą wymagane kwalifikacje, potwierdzone odpowiednimi dokumentami, świadczeń powyżej określonych, w zakresie chorób zębów, jamy ustnej, części twarzowej czaszki oraz okolic przyległych. **Lekarz oraz lekarz dentysta może wykonywać wyżej wskazane czynności, także za pośrednictwem systemów teleinformatycznych lub systemów łączności** (art.2 ust.4 ustawy o zawodach lekarza i lekarza dentysty).

Przez lata obowiązywała wyrażona ustawowo zasada, iż lekarz mógł orzekać o stanie zdrowia tylko po osobistym zbadaniu pacjenta. Obecnie zgodnie z znowelizowanym art. 42 ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty **lekarz orzeka o stanie zdrowia określonej osoby po uprzednim, osobistym jej zbadaniu lub zbadaniu jej za pośrednictwem systemów teleinformatycznych lub systemów łączności.** Lekarz może, bez dokonania osobistego badania pacjenta, wystawić receptę niezbędną do kontynuacji leczenia oraz zlecenie na zaopatrzenie w wyroby medyczne jako kontynuację zaopatrzenia w wyroby medyczne, jeżeli jest to uzasadnione stanem zdrowia pacjenta odzwierciedlonym w dokumentacji medycznej.

Reasumując, nowelizacja z 2015 roku przepisów ustawy o działalności leczniczej oraz o ustawy o zawodach lekarza i lekarza dentysty umożliwia udzielanie świadczeń zdrowotnych, w tym świadczeń lekarskich, na odległość bez osobistego zbadania pacjenta.

TELEKONSULTACJE KARDIOLOGICZNE I GERIATRYCZNE W SYSTEMIE PUBLICZNEGO UBEZPIECZENIA ZDROWOTNEGO

System ochrony zdrowia w Polsce oparty jest na modelu ubezpieczeniowym. Zasady publicznego ubezpieczenia zdrowotnego w Polsce, a także rodzaje przysługujących pacjentom świadczeń określa ustawa z dnia 27 sierpnia 2004 r. o świadczeniach opieki zdrowotnej finansowanych ze środków publicznych(t. jedn. Dz.U. 2018; poz.1510) oraz rozporządzenia wykonawcze wydane na jej podstawie. Świadczeniobiorca (pacjent) w systemie publicznego ubezpieczenia zdrowotnego w Polsce ma prawo do tzw. świadczeń gwarantowanych, Świadczenia gwarantowane to świadczenie opieki zdrowotnej finansowane w całości lub współfinansowane ze środków publicznych. Należą do nich m.in.: podstawowa opieka zdrowotna, ambulatoryjna świadczenia specjalistyczne oraz leczenie szpitalne. Na podstawie Zarządzenia nr 73/2016/DSOZ Prezesa Narodowego Funduszu Zdrowia z dnia 30 czerwca 2016 r. w sprawie określenia warunków zawierania i realizacji umów w rodzaju świadczenia zdrowotne kontraktowane odrębnie telekonsylium kardiologiczne oraz telekonsylium geriatryczne zostały włączone do świadczeń finansowanych ze środków publicznych. Istotą niniejszych świadczeń zdrowotnych jest udzielenie przez lekarza specjalistę konsultacji z zakresu kardiologii lub geriatrii, w czasie rzeczywistym, poprzez zdalną konsultacje w trakcie wizyty pacjenta u lekarza podstawowej opieki zdrowotnej. Powyższe Zarządzenie Prezesa NFZ zostało zastąpione przez Zarządzenie nr 127/2017/DSOZ Prezesa Narodowego Funduszu Zdrowia z dnia 19 grudnia 2017 r. w sprawie określenia warunków zawierania i realizacji umów w rodzaju świadczenia zdrowotne kontraktowane odrębnie (zostało ono uchylone z dniem 12 maja 2019, kiedy weszło w życie nowe Zarządzenie). Obecnie obowiązuje w przedmiotowym zakresie Zarządzenie nr 45/2019/DSOZ Prezesa Narodowego Funduszu Zdrowia z dnia 11 kwietnia 2019 r. w sprawie określenia warunków zawierania i realizacji umów w rodzaju świadczenia zdrowotne kontraktowane odrębnie. Sama idea telekonsylium jako świadczenia odrębnie kontraktowanego przez NFZ w poszczególnych Zarządzeniach nie uległa zmianie, natomiast zmieniły się podstawy prawne.

Choroby układu krążenia są główną przyczyną zgonów w Polsce. Średnio rocznie szacuje się, że choroby układu krążenia odpowiadają za 45,8% zgonów[17]. Mimo znacznego zmniejszenia liczby zgonów w ciągu ostatnich 25 latach, standaryzowany współczynnik zgonów z powodu chorób sercowo-naczyniowych w Polsce wciąż jest większy niż w większości krajów Unii Europejskiej w 2012 roku wyniósł 652,4. Ocenia się, że jeśli nie zostaną podjęte poważne zmiany w zakresie profilaktyki i leczenia chorób układu krążenia, odsetek Polaków umierających będzie w najbliższych latach wzrastał, i w 2050 roku może osiągnąć poziom 51%.

Telekonsylium kardiologiczne obejmuje wywiad, analizę zapisu EKG, interpretację wyników badań oraz ustalenie planu leczenia. Według stanu na rok 2018 telekonsylium kardiologiczne zostało zakontraktowane na terenie czterech województw (dolnośląskiego, małopolskiego, mazowieckiego i podkarpackiego) z dwunastoma świadczeniodawcami. W województwie dolnośląskim wartość umów wyniosła 7 170,00zł, w małopolskim 75000,00zł, w mazowieckim 132 622,88zł, zaś w podkarpackim 20 700,00 zł [18].

Starzenie się społeczeństw, jak również niekorzystne prognozy społeczno-demograficzne na najbliższe lata, wymuszają zmiany i stawiają nowe wyzwania dla współczesnego modelu systemu opieki zdrowotnej. W populacji osób starszych nieuchronnie wzrasta zapotrzebowanie na usługi zdrowotne. Pomocna w przedmiotowym zakresie może być telegeriatria. Telemedyczna opieka geriatryczna wykorzystuje nowoczesne technologie transferu danych medycznych oraz obrazowych do ośrodków konsultacyjnych, a także systemy zdalnego kontaktu z osobami wymagającymi stałego nadzoru medycznego w codziennym środowisku.

Telekonsylium geriatryczne dotyczy pacjentów po 65. roku życia i obejmuje: zdalny wywiad, zdalną analizę badań EKG, zdalną analizę badań diagnostycznych, zdalną analizę leczenia farmakologicznego oraz optymalizację leczenia. Telekonsylium geriatryczne zostało zakontraktowane tylko i wyłącznie na terenie województwa małopolskiego. Umowy zostały zawarte z dwoma świadczeniodawcami na łączną kwotę 59 384,00zł.

Zgodnie z Zarządzeniem nr 45/2019/DSOZ Prezesa Narodowego Funduszu Zdrowia świadczenia udzielone w zakresie:

Tabela. I. Rodzaje świadczeń telemedycznych i ich podstawy prawne

Lp.	Rodzaj świadczenia zdrowotnego	Podstawa prawna
1	Każde świadczenie zdrowotne udzielane przez podmiot leczniczy lub praktykę zawodową za pośrednictwem systemów teleinformatycznych lub systemów łączności	Art. 3 ust.1 ustawy z dnia 15 kwietnia 2011 roku o działalności leczniczej
2	Telekonsultacje lekarskie (obejmujące w szczególności: badanie stanu zdrowia, rozpoznawanie chorób i zapobieganie im, leczenie i rehabilitacje chorych oraz udzielanie porad lekarskich)	Art. 2 ust.4 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty
	Badanie lekarskie za pośrednictwem systemów teleinformatycznych lub systemów łączności	Art.42 ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty
3	Telekonsylium kardiologiczne finansowane przez NFZ	Zarządzenie aktualne Prezesa Narodowego Funduszu Zdrowia (obecnie Nr 45/2019/DSOZ)
4	Telekonsylium geriatryczne finansowane przez NFZ	Zarządzenie aktualne Prezesa Narodowego Funduszu Zdrowia (obecnie Nr 45/2019/DSOZ)

Źródło: opracowanie własne na podstawie obowiązującego prawa (stan prawny na dzień 21 maja 2019)

1. telekonsylium kardiologiczne sprawozdawane i rozliczane są przez świadczeniodawcę zatrudniającego lekarza specjalistę w dziedzinie kardiologii, biorącego udział w konsylium lekarskim odbywającym się z zastosowaniem sprzętu telemedycznego;
2. telekonsylium geriatryczne sprawozdawane i rozliczane są przez świadczeniodawcę zatrudniającego lekarza specjalistę w dziedzinie geriatrii, biorącego udział w konsylium lekarskim odbywającym się z zastosowaniem sprzętu telemedycznego.

Maksymalna liczba świadczeń udzielonych jednemu świadczeniobiorcy w każdym z powyższych zakresów wynosi jedno telekonsylium nie częściej niż raz na 30 dni i nie więcej niż 4 telekonsylia w roku.

Wprowadzenie nowych świadczeń gwarantowanych, tj. telekonsylium kardiologicznego i geriatrycznego, daje mnóstwo korzyści, nie tylko pacjentom, ale również lekarzom POZ. Pacjenci, nierzadko mieszkający w odległych miejscach od ośrodków specjalistycznych zyskają oszczędność czasu, związaną z przemieszczaniem się oraz większe bezpieczeństwo fizyczne i psychiczne swojego zdrowia. Mogą mieć świadomość, że w razie konieczności mogą poprzez telekonsulatcje zasięgnąć porady lekarskiej, a bariera odległości przestaje mieć znaczenie. Lekarze POZ natomiast zyskają niezbędną pomoc w konsultacji trudnych przypadków od specjalistów z większych ośrodków.

Telemedycyna kardiologiczne i geriatryczne należy uznać za krok w dobrym kierunku, jako że zwiększają dostępność do świadczeń zdrowotnych. Pacjent nie musi od razu kierować się do lekarza specjalisty – wystarczy umówienie się na wizytę do lekarza POZ. Dodatkowo zakłada się ścisłą współpracę pomiędzy Podstawową Opieką Zdrowotną a opieką specjalistyczną. Jednakże problemem, jak się okazało w praktyce, jest bardzo mała liczba chętnych świadczeniodawców do udzielania przedmiotowych świadczeń zdrowotnych i zasady ich finansowania (m.in. brak zachęt finansowych dla lekarzy POZ do korzystania z takich konsultacji).

PODSUMOWANIE

Należy przyjąć, że telemedycyna nie powinna być postrzegana jako odrębna gałąź medycyny. Stanowi bowiem innowacyjną formę sprawowania opieki medycznej przy wykorzystaniu systemów teleinformatycznych lub systemów łączności. Dzięki temu każda specjalizacja medycyny może sięgać po rozwiązania telemedyczne.

Dzięki rozwojowi telemedycyny możliwe jest przełamywanie przez personel medyczny barier geograficznych, postawienie szybkiej diagnozy i zapewnienie opieki medycznej poprzez transfer informacji zamiast konieczności przemieszczania się pacjentów, szczególnie tych, którzy z różnych powodów nie są w stanie fizycznie przybyć na tradycyjną wizytę do lekarza. Ocenia się, że stanie się ona w najbliższym czasie jednym z najważniejszych instrumentów ochrony zdrowia ze względu na rozwój nowoczesnych technologii umożliwiających przesyłanie danych, a także z uwagi na współcześnie tendencje socjologiczne(m.in. starzenie się społeczeństwa, choroby cywilizacyjne wymagające stałego monitoringu).

Konkludując, aktualnie obowiązujące w Polsce prawo umożliwia rozwój telemedycyny i udzielanie konsultacji telemedycznych przez lekarzy. Fundamentalną regulacją prawa polskiego wprowadzającą możliwość wykonywania zawodów medycznych w tym zawodu lekarza w sposób „telemedyczny" jest art. 3 ustawy o działalności leczniczej, który jednoznacznie wskazuje na możliwość wykonywania działalności leczniczej w sposób „telemedyczny", czyli za pośrednictwem systemów teleinformatycznych. Także ustawa o zawodach lekarza i lekarza dentysty dopuszcza, by świadczenie zdrowotne lekarskie mogło być udzielane w sposób „telemedyczny". Tabela I przedstawia rodzaje świadczeń telemedycznych bezpośrednio określonych przez polskiego prawodawcę i ich konkretne podstawy prawne.

W Polsce finansowane są przez NFZ dwie procedury typowo lekarskie związane z telemedycyną tj.: telekonsylium kardiologiczne i telekonsylium geriatryczne. Obejmują one telekonsultację pomiędzy lekarzem POZ a odpowiednio

lekarzem (specjalistą) kardiologiem i geriatrą. Możliwość refundowanych telekonsultacji, ułatwia nie tylko pacjentom mieszkającym w mniejszych miastach i na wsiach dostęp do leczenia specjalistycznego, ale również umożliwia lekarzom POZ konsultacje trudnych przypadków. Obecnie nie istnieją prawne przeszkody utrudniające praktyczną realizację wymienionych procedur telemedycznych.

W praktyce polskiego systemu ochrony zdrowia w aspekcie finansowania istnieją dwa rodzaje rozwiązań telemedycznych tj. finansowane ze środków publicznych oraz komercyjne (finansowane przez pacjenta/klienta). Niektóre rozwiązania są współfinansowane ze środków Unii Europejskiej.

Reasumując, obecnie wykorzystywanie w Polsce telemedycyny w pracy lekarza opiera przede wszystkim na trzech filarach(zakresach), tj.:

1. telekonsultacjach,
2. telediagnostyce,
3. teleedukacji.

Dziedzinowo najbardziej rozwija się w Polsce od lat telekardiologia, szczególnie w zakresie zdalnego monitorowania pacjenta (teleEKG) oraz teleradiologia w zakresie zdalnego opisywania badań RTG, TK, MRI. W praktyce polskiej, jak i światowej telemedycyny najczęściej mamy do czynienia ze zdalnym monitorowaniem pacjenta – polega ono na bezpiecznym przesyłaniu danych do analizy przez specjalistę znajdującego się w innej lokalizacji.

Za podstawowe bariery rozwoju telemedycyny w Polsce należy uznać bariery personalne (zarówno ze strony lekarzy bojących się innowacji czy też mających problemy z opanowaniem nowych technologii, jak też pacjentów, szczególnie starszych, niemających zaufania do leczenia „na odległość"), a także bariery technologiczne-brak odpowiednich efektywnych rozwiązań technologicznych oraz bariery ekonomiczne (potrzeba wysokich nakładów finansowych na wdrożenie systemów telemedycznych).

Telemedycyna, należy do technologii, które bezspornie w znacznym stopniu przyczyniają się do poprawy dostępności udzielanych świadczeń. W przyszłości stanie się ona standardowym elementem usług medycznych i będzie niezbędna do prawidłowego funkcjonowania systemów ochrony zdrowia. Telekonsultacje lekarskie stanowią jedną z najpotrzebniejszych usług rynku medycznego, która wymaga upowszechnienia.

PIŚMIENNICTWO

1. Karkowski T. Telemedycyna i eHealth w sektorze opieki zdrowotnej(online); https://sip.lex.pl/#/publication/469834535/karkowski-tomasz-telemedycyna-i-e-health-w-sektorze-opieki-zdrowotnej? (dostęp 27.12.2018).
2. Lops K. Cross-border telemedicine. Opportunities and barriers from an economical and legal perspective. Rotterdam: Erasmus University - Institute of Health Policy and Management; 2008.
3. www.americantelemed.org/i4a/pages/index.cfm? (dostęp 23.12.2018).
4. Martyniak J. Podstawy informatyki z elementami telemedycyny. Kraków: Wydawnictwo Uniwersytetu Jagiellońskiego; 2009.
5. Ferrer-Roca O, Sosa-Iudicissa M. Handbook of Telemedicine. Amsterdam: IOS Press; 1999.
6. www.ncbi.nlm.nih.gov/pmc/articles/PMC1422462 (dostęp 27.12.18).
7. Zubrzycki J, Małecka-Massalska T. Telemedycyna–medycyna i technika w walce o nasze zdrowie. Zdr. Publ. 2010; 120 (4): 421-425.
8. http://www.ptl.medserwis.pl (dostęp 23.12.2018).
9. https://www.telemedycyna.org (dostęp 23.12.2018).
10. Jankowski M, Wieczorek A et al. Telemedycyna w Polsce, możliwości i szanse rozwoju, Warszawa: Fundacja im. Lesława Pagi; 2016.
11. Olszanowski R, Gierek R, Skrzypek M. Raport uwarunkowania rozwoju telemedycyny w Polsce. Warszawa: Krajowa Izba Gospodarcza; 2016.
12. Jankowski M, Wieczorek A et al. Telemedycyna w Polsce, możliwości i szanse rozwoju, Warszawa: Fundacja im. Lesława Pagi; 2016.
13. https://telemedycynapolska.pl/rozwiazania/calodobowy-zdalny-monitoring/(dostęp z 21.05. 2019).
14. https://teleradiologiahig24.pl/(dostęp z 21.05.2019).
15. http://teleopieka.com.pl/(dostęp z 21.05.2019).
16. Paszkowska M. Telemedycyna - podstawowe regulacje prawne. Ogóln Przegl Med.2018;3:54-59.
17. Główny Urząd Statystyczny. Zachorowalność i umieralność na choroby układu krążenia a sytuacja demograficzna Polski (dostęp 27.12.2018). www.stat.gov.pl.
18. www.nfz.gov.pl/o-nfz/informator-o-zawartych-umowach (dostęp 27.12.2018).

Konflikt interesów:
Autorka deklaruje brak konfliktu interesów.

AUTOR KORESPONDUJĄCY
Małgorzata Paszkowska
Wyższa Szkoła Informatyki i Zarządzania w Rzeszowie
Katedra Zarządzania
ul. Sucharskiego 2, 35-225 Rzeszów
e-mail: mpaszkowska@wsiz.rzeszow.pl

Nadesłano: 17.04.2019
Zaakceptowano: 23.05.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

ADMINISTRATIVE AND LEGAL ENFORCEMENT OF HEALTH CARE: CONCEPTUAL FRAMEWORKS

Igor Gladchuk, Olena Terzi
ODESA NATIONAL MEDICAL UNIVERSITY, ODESA, UKRAINE

ABSTRACT

Introduction: The analysis of the administrative and legal enforcement of health care in Ukraine indicates the lack of sufficient regulatory and legal acts due to the lack of and deficiencies in conceptual documents, doctrinal developments, strategic planning in this area. The modern administrative-legal management is historically due, since during the Soviet period health care regulation was determined by the high centralization of governance, the imperative of decision-making, the precise regulation of the activities of its subjects, the lack of overall control and supervision.

The Conceptual Frameworks in this area, as shown by the analysis of scientific literature and legal documents, should include general provisions, goals, objectives, principles, legal framework, subject and object, priority areas of implementation, phases and stages, terms, amount of financial, material and technical resources, expected results.

Each component of the Conceptual Frameworks should be scientifically verified, confirmed by practical experience and statistical data, and also to correspond to the real state of health care in Ukraine. Interconnectivity and intersectionality of the structural parts of the Conceptual Frameworks will ensure its effectiveness.

KEY WORDS: health care, administrative and legal enforcement, conceptual frameworks, purpose and tasks in the area of health care, laws of Ukraine

Wiad Lek 2019, 72, 7, 1350-1353

INTRODUCTION

The concept of administrative and legal enforcement of health care is a guiding document that should contribute to the development of perspective goals and objectives in this area aimed at streamlining and improving medical activities, providing a high level of medical care, other medical services to the population, prolonging life and improving the health of a man. The implementation of conceptual purpose and objectives that are established in accordance with the type of medical activity or medical care is carried out by public authorities and other non-state institutions within their competence and competence in the area of health care. The effectiveness of the realisation of any concept depends on the appropriateness and priority of the selected areas of achievement of predicted and expected results, efficiency and effectiveness of administrative and legal means and administrative and legal regulation.

Ukraine has long been developing concepts in the medical sphere, it is the Concept for the development of public health care in Ukraine, the Concept of financing health care system in Ukraine, the Concept for the development of the system of public health protection of Ukraine, the Concept of management of quality of health care in the area of health care Ukraine, Concept of Informatization in the area of health care Ukraine and some others. Their realisation is provided by plans of measures approved by government decrees or orders of the Ministry of Health Of Ukraine. However, the Concept of administrative and legal enforcement for this area is proposed for the first time before implementation.

MATERIALS AND METHODS

In order to establish the objectivity and validity of scientific statements, conclusions, during the research used a set of general scientific and special scientific methods, in particular, such as: the formal legal method was used to determine the general provisions of the Conceptual Frameworks; by the comparative legal method the task of the subjects of executive power in the area of health protection was clarified, the method of forecasting and modeling was used to establish the terms of implementation of the Conceptual Frameworks; the method of system analysis allowed to study the priority directions of the implementation of the Conceptual Frameworks; the historical-legal method has allowed to reveal the features of the phases and stages of the Conceptual Frameworks. There has also been used the scientific-heuristic potential of such philosophical methods of research as analysis, synthesis, deduction, induction, abstraction, etc.

REVIEW AND DISCUSSION

The general provisions of the constituent elements should include information on the state of health and life expectancy of citizens, the quality of provision of medical services, including at the primary level; resource efficiency; expediency of the system of remuneration of doctors and other employees in this area. The general provisions should include indication of the main directions of public health policy, namely: step-by-step increase of state allocations to this sphere, their effective use; intensive development of the medical and pharmaceutical industry, etc.[1]

The purpose and objectives of the Conceptual Frameworks are in line with the law purposes and objectives int the area of healthcare, based on the fact that they have a common goal, tasks, objects and subjects of activity.

The aim of the Conceptual Frameworks is to create a health system that would ensure a high standard of living for the population, provide quality medical care, and guarantee the protection of human rights and interests in the medical sphere.

To the general tasks of the Conceptual Frameworks we include:

1) analysis and assessment of the state of the administrative and legal provision of health care, including the identification of problems and disadvantages that need to be eliminated;
2) the development and implementation of a system of management and organizational measures to improve the administrative and legal enforcement of health care;
3) realisation of the developed measures in accordance with the defined directions of the Conceptual Frameworks;
4) implementation of control and supervisory functions in order to ensure the effectiveness of the expected results;
5) improvement of the departmental legal and regulatory framework on the competence and authority of health care providers in the organization of medical activities and medical care, licensing and control.

Defining the principles of the Conceptual Frameworks, we would mention that they must include: 1) general principles in the area of health care; 2) principles of realization of the state policy in a concretely defined sphere of health care; 3) the principles of administrative and legal provision of health care; 4) principles that will contribute to the development of the Conceptual Frameworks; 5) principles of implementation of the Conceptual Frameworks.

The legal basis for the Conceptual Frameworks is legislative and subordinate acts. To the legislative base we include: the Constitution of Ukraine and the laws of Ukraine in the area of health care. Article 3 of the Constitution of Ukraine, man, his life and health, honor and dignity, inviolability and security are proclaimed the highest social value. Article 27 establishes the inalienable right of every person to life. No one can be arbitrarily deprived of life. The duty of the state is to protect human life. Everyone has the right to protect his life and health, life and health of others from unlawful encroachments. Article 49 establishes the right of everyone to health care, medical care and health insurance. Health care is provided by state financing of the relevant socio-economic, health and sanitation and health-prevention programs [6].

The regulatory framework also includes departmental acts that clarify and concretize legislative provisions on competence, function, task, direction, and specifics of the subject matter of the Conceptual Frameworks. Rulemaking activity has its goals to ensure: legal consolidation of existing relations in this area and their legal regulation; formation of new relations, desirable or necessary in terms of performance of perspective tasks; elimination of relations and situations, outdated and inhibiting the development of progressive tendencies [2].

The subjects of the implementation of the Conceptual Frameworks are: the supreme bodies of state power, including the legislative and executive (the President of Ukraine, the Verkhovna Rada of Ukraine, the Cabinet of Ministers of Ukraine), who exercise authority in the area of health care; a special central executive body (Ministry of Health of Ukraine); other central bodies of executive power in the sphere of health care, central executive authorities, which are subject to health care institutions, local state administrations and local self-government authorities.

The Verkhovna Rada of Ukraine adopts laws on the functioning of the medical sector, approves national programs on public health and the principles of the relevant state policy, examines the reform of the health care system, and conducts parliamentary hearings on the state of health care in Ukraine.

The general guidance in the of area health care is the authority of the President of Ukraine, namely, the Head of the State bears personal responsibility for the implementation of the relevant state policy, through the system of state executive bodies ensures the implementation of the national policy in this area, and exercises other powers provided for by the Constitution of Ukraine.

The Cabinet of Ministers of Ukraine directs and coordinates the activities of central and local government bodies in shaping and implementing state policy in the field of health care; annually reports on implementation of state policy to the VRU, organizes the development and implementation of national programs in the area of health care, concludes intergovernmental agreements, coordinates international cooperation on health care issues.

The Ministry of Health of Ukraine is the main authority in the system of central bodies of executive power, which ensures the formation and implementation of state policy in the field of health care, protection of the population from infectious diseases, the fight against HIV / AIDS and other socially dangerous diseases, ensures formation and implementation of state policy in the field of creation, production, quality control and sale of medicines, medical immunobiological preparations and medical products, in the sphere of narcotic drugs circulation, psycho tropical substances, their analogues and precursors, counteraction to their illicit circulation, etc. [3].

The authority and competence in the field of public health of the Ministry of Defense of Ukraine, the Ministry of Internal Affairs of Ukraine, the Security Service of Ukraine, the Ministry of Infrastructure of Ukraine and other ministries and departments are established by the relevant legislative acts.

The local state administration in the area of health care: implements relevant state policies and national programs; implements measures to preserve the network of such institutions; develops forecasts for their development; takes measures to prevent infectious diseases, epidemics, epizootics and their elimination; organizes the work of medical institutions to provide assistance to the population, provides the established benefits and assistance related to the protection of maternity and childhood, improving the living conditions of large families [7].

The executive bodies of village, settlement and city councils manage the health care institutions and health institutions, organize health care and nutrition in educational, cultural, physical education and sports institutions, and health facilities owned by territorial communities; provide within the given authority of the bodies the availability and free of charge medical services in the respective territory; development of all types of medical care; development of a network of medical institutions of all forms of ownership; provide, in accordance with the legislation, privileged categories of the population with medicinal products and medical products [8].

The system of entities in this area is a combination of state and non-state authorities, their officials and managers who directly or indirectly participate in the management process for ensuring the effectiveness of health care. Their powers are defined and carried out in accordance with legislative and regulatory acts rather widely, but for the most part they are not sufficiently specified.

The object of administrative and legal enforcement is a system of measures carried out by public authorities and local self-government bodies, their officials, health care institutions, individual entrepreneurs who are registered in the manner prescribed by law and received a license for the right to conduct economic activities from medical practice, medical and pharmaceutical workers, public associations and citizens in order to preserve and restore physiological and psychological functions, optimal disability and social activity of a person with the maximum biologically possible individual duration of her life [4].

The priority areas for the implementation of the Conceptual Frameworks are:

legal and organizational provision of state comprehensive and targeted health care programs, including on the development of primary health care on the basis of family medicine;

realization of measures on restructuring of medical industry and its informatization, improvement of licensing of medical activity and medical aid; raising the level of health care in Ukraine to relevant foreign experience and practice;

elimination of problems and disadvantages of the state of administrative-legal protection of health care, namely: lack of coordination and interaction of state bodies of executive power, local self-government bodies, medical institutions; disadvantages of licensing medical practice and medical practice;

assistance in improving the subordinate legal and regulatory framework for the organization of medical activities and medical care.

Stages and Phases of the Conceptual Framework are defined according to each direction and type of activity with the approval of the general term. Installed in most: preparatory stage, implementation stage, integration stage.

As to the terms of implementation of the Conceptual Frameworks, we will point out the complexity of their definition on the following grounds: first, they can be determined for each stage and phase, the failure of one period will lead to the failure of the following; second, the tasks at each stage or stage depend on their financial and logistical support; and thirdly, their implementation is conditioned by the general socio-economic situation in the country. It is impossible to set concrete and imperative deadlines for the implementation of the Conceptual Foundations, therefore, in most cases they are determined tentatively.

The volume of financial, material and technical resources must made up of funds from the state and local budgets, funds of compulsory state social medical insurance and voluntary medical insurance, funds of accumulation funds of territorial communities and charitable foundations, charitable donations and donations of legal and natural persons, funds received for providing paid medical services, and sources aren't prohibited by law [1].

Expected results. The practical implementation of the Conceptual Frameworks will enable Ukraine to guarantee the proper level of human health and longevity, obtaining quality medical care and its compliance with international standards. The result of the Conceptual Frameworks must maximize full, timely and prompt response to possible challenges in this area.

CONCLUSIONS

The Conceptual Frameworks of the administrative and legal enforcement of health care are developed within the framework of a unified state policy in the medical sphere; formation of the administrative-legal base of health care is provided by the legislative authority; organization, protection, development of social relations is carried out by the activities of competent entities through the use of administrative and legal means.

The Conceptual Frameworks in this area include its purpose, objectives, principles, legal framework, subject and object, priority directions of implementation, stages and stages, terms, scope of financial, material and technical resources, expected results. Each component of the Conceptual frameworks has its own meaning and function.

The Conceptual Frameworks are general, fundamental and define the priorities of Ukraine's medical policy for the long-term perspective. The Conceptual Frameworks will contribute and form the basis for developing program documents and regulations on improving, protecting and protecting the life of the population, improving the level of health and life expectancy of a person, as well as state policy in the medical sphere.

REFERENCES

1. Pro Kontseptsiiu rozvytku okhorony zdorovia naselennia Ukrainy: Ukaz Prezydenta Ukrainy vid 7.12.2000 N 1313/2000 URL: https://zakon.rada.gov.ua/laws/show/1313/2000
2. Vovk O. Kontseptsiia natsionalnoi bezpeky: teoretychnyi aspect. URL: http://pidruchniki.com/ 17910211/politologiya/ponyattya_zmist_kontseptsiyi_natsionalnoyi_bezpeki [in Ukrainian]
3. Pro zatverdzhennia Polozhennia pro Ministerstvo okhorony zdorovia Ukrainy: Postanova Kabinetu Ministriv Ukrainy vid 25.03.2015 № 267 URL: http://zakon3.rada.gov.ua/laws/show/267-2015-%D0%BF

4. Osnovy zakonodavstva Ukrainy pro okhoronu zdorovia: Zakon Ukrainy vid 19.11.1992 № 2801-XII URL: https://zakon.rada.gov.ua/laws/card/2801-12
5. Pro Kontseptsiiu rozvytku okhorony zdorovia naselennia Ukrainy: Ukaz Prezydenta Ukrainy vid 7.12.2000 N 1313/2000 URL: https://zakon.rada.gov.ua/laws/show/1313/2000
6. Konstytutsiia Ukrainy vid 28.06.1996 № 254k/96-VR URL: https://zakon.rada.gov.ua /laws/card/254%D0%BA/96-%D0%B2%D1%80
7. Pro mistsevi derzhavni administratsii: Zakon Ukrainy vid 09.04.1999 № 586-XIV URL: http://zakon5 .rada.gov.ua/laws/show/586-14
8. Pro mistseve samovriaduvannia v Ukraini: Zakon Ukrainy vid 21.05.1997 № 280/97-VR URL: http://zakon0.rada.gov.ua/laws/show/280/97-%D0%B2%D1%80/page

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Olena Terzi
Odesa National Medical University
Odesa, Ukraine
tel: 380934307777
e-mail: terzi.elena@ukr.net

Received: 10.04.2019
Accepted: 14.06.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

RELEVANT ISSUES OF THE CRIMINAL LIABILITY OF THE PRIVATE DOCTORS FOR CORRUPTION CRIMES

Olha S. Bondarenko, Volodymyr V. Pakhomov, Sergey V. Saulyak, Mykhailo O. Dumchikov
SUMY STATE UNIVERSITY, SUMY, UKRAINE

ABSTRACT

Introduction: Corruption, as a socio-economic problem, is characteristic of every society.

The aim: To study relevant issues of criminal liability of the private doctors for committing corruption crimes.

Materials and methods: In the article general scientific and special-scientific methods of cognition wer eused which provided an objective analysis of the research purpose.

Review: The article analyzes actual questions of relenant issues of criminal liability of the private doctors for committing corruption crimes. The authors propose to research the criminal responsibility of this specific subject through the prism of the crime, as well as it's elements. Thus, special attention is focused on the analysis of thees sence of the object of the crimes, the responsibility for which provided in. Art. 365-2 and 368-4 of the Criminal Code of Ukraine. Inaddition, the concept of "unlawful profit" is investigated, in the context of comparison with the "bribe". Thees sence of the objective side of corruption crimes, the subject of which is a private doctor, is explained in detail. In particular, the concepts of "authority", "offer", "promise", etc. Particul arattention is paid to analyzing the legal status of a private doctor as a person authorized to provide public services. The authors focus on the analysis of the subjective side of thes corruption crimes being studied by a private physician. All penalties that can be applied to a private doctor for committing corrupt acts are systematized. At the very end, the issue of the totality of crimes is investigated.

Conclusions: Bringing a private doctor in the responsibility for committing a corrupt act is difficult in there gion, because the criminalization of corruptionactions of suchpersons took place relatively recently, therefore, pre-trial investigation bodies have not yet established a well-established system of tactical and methodological actions that would facilitate this process.

KEY WORDS: criminal liability, corruption crimes, private doctors

Wiad Lek 2019, 72, 7, 1354-1358

INTRODUCTION

Corruption, as a socio-economic problem, is typical of every society. At the same time, the level of corruption in each state varies and depends on the economic, social, political, cultural, moral and psychological development of society like general and individual citizens in particular. Unfortunately, nowadays Ukraine, according to the rating published by Transparency International, is one of the most corrupt countries in the world [1]. According to social studies, one of the most favorable spheres of society's life for thecorruption development, after the scope of pre-trial investigation and judicial review, is the medical sphere. Corruption in the area of providing health care and medical care is extremely dangerous. We have to emphasize, that firstly, corruption violates the constitutional prescription, set forth in art. 49 of the Fundamental Law of Ukraine [2]; and secondly, the provisions of art. 21 of the Law of Ukraine "On Labor Remuneration", according to which the employee has the right for pay for his work in accordance with the acts of the law and the collective agreement on the basis of the concluded employment contract [3]. Important in the context of this argument can be considered the provision of medical services falls according to competence of the competent entity, that is, it is obliged to provide them. Moreover, such a person should exercise his powers by providing high-quality and rapid public services. Thus, any attempts or actions committed for the purpose of "encouragement" or "gratitude" to the competent entity are unlawful, since they discredit the basic principles of labor legislation.

ANALYSIS OF RECENT RESEARCH AND PUBLICATIONS

As for the scientific development of this problem, the study of corruption and corruption was committed, in particular, by such teachings as Yu. Grodetsky, O. Zakharchuk, M. Melnyk, A. Savchenko, T. Slutsk, V. Ttiugin, M. Khavronyuk and others. At the same time, the study devoted exclusively to the relevant issues of criminal liability of private doctos for corruption crimes was not implemented.

THE AIM

The aim of the article consists in research of relevant issues of criminal liability of private doctors for corruption crimes.

MATERIALS AND METHODS

The article uses general scientific and special-scientific methods of cognition, which provided an objective analysis

of the research purpose. Taking into account the specifics of the topic, the main aims and objectives of the study, the dialectical method was first used, which outlines the methodological principles of the study and specifies the essence of the analyzed concepts as criminal-law categories; the method of scientific analysis and generalization used to identify and systematize theoretical foundations of the investigation of the criminal liability of a private doctor for committing corruption crimes; the formal legal method was used to clarify the structure and ratio of the concepts studied, as well as to study the relevant provisions of the Ukrainian legislation on criminal liability for crimes in the field of service activities and professional activities related to the provision of public services. For the in-depth study of the normative provisions on the criminal liability of a private doctor for committing corruptive crimes, a systemic and structural method was used, comparing them with other provisions of the current Criminal Code of Ukraine. These and other research methods were used in the work in the relationship and interdependence, which ensured the completeness and completeness of the research, the reliability of the scientific results obtained.

REVIEW AND DISCUSSION

The legal basis for the legal liability of a private doctor for corruption crimes (that is, socially dangerous acts that encroach upon the criminal law protection of relations in the field of providing public services for which the subject of crime is brought to the established criminal liability law [4 p. 37]) is the Criminal Code Of Ukraine. Thus, the legislator criminalized the abuse of authority by persons providing public services (Article 365-2 of the Criminal Code of Ukraine) and bribing the person who provides public services (Article 368-4 of the Criminal Code of Ukraine). The subject of these crimes is the person providing the public service. Public services are services provided by the public sector (ie public authorities, local governments, enterprises, institutions and organizations of state and communal ownership), and in some cases, the private sector is under the responsibility of the public sector (public authority) and, as a rule, at the expense of public funds (that is, funds from the state and local budgets) "[5, p. 43]. Public services are characterized by the following features: they are aimed at protecting and ensuring conditions for the realization of public interests, rights and interests of legal and natural persons; give rise to legal consequences; the procedure and form of their provision are determined by the state or a body of local self-government [6, p. 862]. In accordance with Part 1 of Art. 3 of the Law of Ukraine "On the Fundamentals of Ukrainian Health Law", a medical service is a service provided to a patient by a healthcare institution or a sole proprietor who has been registered and has received a license for the conduct of economic activity in medical practice in accordance with the procedure established by law (private doctor), and paid by the customer. The customer of health care services may be the state, relevant local governments, legal and physical persons, including the patient [7]. Moreover, according to pp. 226 p. 1 tbsp. 14 of the Tax Code of Ukraine, persons who provide public services must recognize self-employed persons who are not only entrepreneurs but also conduct independent professional activities, in particular private doctors, provided that such persons are not employees or sole proprietors and use them hired labor no more than four individuals [8]. Thus, it follows from the analysis of the legislation that the medical service is public service.

According to Part 2 of the Art. 2 of the Criminal Code of Ukraine, the only ground for criminal liability is the presence in the act of a person of the characteristics of the crime [9]. Composition of a crime - a collection of objective (object and objective side), as well as subjective (subject and subjective side) elements that determine a socially dangerous act as a criminal.

The first element of the composition of corruption crimes that may be committed by a private physician is their object, that is, certain social relations, that get harm or the threat of causing such damage. And in this case, it is social relations that arise in connection with the activity of the official in accordance with the regulatory acts, which constitutes the proper work of the state apparatus and the apparatus of local self-government, associations of citizens, enterprises, institutions and organizations independently from forms of ownership, as well as individuals-entrepreneurs and self-employed persons [10, p. 7].

A special place in the structure of the object of crimes, the responsibility for the commission of which is provided for in Art. 365-2 of the Criminal Code of Ukraine and Art. 368-4 of the Criminal Code of Ukraine, there is their subject - those things of material and / or immaterial world to which the offender directly affects the process of a socially dangerous attack and through direct influence on which he acts on the object of the crime. So, the subject of these crimes is unlawful benefit. This concept is not legislative innovation any more, while the public continues to operate on the notion of "bribe", which differs from "unlawful benefit" not only in form but also in essence. Since the "bribe" has always been interpreted by the legislator and judicial practice, as solely material things, for example, property, money. Instead, the essence of "unlawful benefits" is much more wider, because it has not only cash or other property but also benefits, benefits, services, intangible assets, any other benefits of intangible or non-monetary nature. The content of these terms is interpreted in other normative acts or in doctrinal sources, which in fact are not sources of criminal law. Therefore, it is urgent to update the legislation in order to clarify these concepts for the criminal-law and anti-corruption sphere [11, c. 10].

Regarding the objective aspect of the analyzed corruption crimes, it is an explicit aspect of the crime. It defines: the essence of the crime; the way of its commission; conditions, place, time, circumstances of committing a crime, use of a tool or instrument [6, c. 15]. So, in essence, the crimes, the responsibility for the commission of which is provided for in Art. 365-2 of the Criminal Code of Ukraine and Art. 368-4 of the Criminal Code of Ukraine, are committed in

an active form, that is by way of action: abuse of authority and acceptance of a proposal, acceptance of a promise and obtaining an illegal benefit. The concept of "abuse of authority" is not new to a criminal law, but, given the systemic and complex changes in anti-corruption legislation, needs to be analyzed in detail. In the criminal legal literature it is noted that abuse of powers is the realization of factual and legal possibilities, committed contrary to the purpose, tasks, interests of legal activity, when acts are committed within the limits of the powers granted, but it is unlawful or deliberate not to commit certain actions that must to be done. Unlike excess of power and official powers, abuse of authority, a person does not go beyond the respective rights and powers [12, p. 308]. As to the essence of the concept of "authority", then, in the opinion of P Lyubchenko, they have the rights and responsibilities that are assigned to a particular special subject, and it is with the specific authority that the person providing the public service has to implement the appropriate competence, which in turn is a set of subjects of authority and authority [13, p. 28]. Crime envisaged by Art. 365-2 of the Criminal Code of Ukraine, is is considered complete from the moment of causing significant harm to the rights protected by the law or interests of individual citizens, public or public interests or interests of legal entities. Significant damage should be regarded as such harm, which is 100 times more than the non-taxable minimum income of citizens. That is, considering the wording of the concept of "substantial harm", the legislator interprets it solely through the material (monetary) form. Thus, A. Savchenko proposes to consider: 1) the losses incurred by a person in connection with the destruction or damage to the thing, as well as the expenses that a person has or should do to restore his violated right (actual damage); 2) income that a person could actually receive in normal circumstances, if his right was not violated (loss of profit). In this case, the amount of monetary compensation for non-pecuniary damage can not be included in the content of substantial harm (as well as grave consequences) [14, c. 92].

Of particular scientific interest, of course, represents the interpretation of the concepts "offer" and "promise", which are relatively new to the criminal law. Thus, under the proposal of unlawful benefit should be understood , the consent of the private doctor regarding the intention to transfer or to grant him unlawful benefit for the commission or non-execution of any action using his authority or official position and may be carried out in any form (oral, written, SMS-message, etc.) [15, p. 42]. Accordingly, the promise made by a private physician to grant him unlawful benefit is to identify him / her to accept such a benefit in response to a statement made by the person promising it, with the intention of providing it with a statement of the time, place and manner of providing such benefit, and provides for the adjustment of the amount, form or type of unlawful benefit [16, p. 26].

Introduction of criminal liability for the mere fact of accepting an offer (promise) of unlawful benefit deprives a private doctor of further abandoning his criminal intentions. Therefore, it is not excluded that a private doctor may agree to accept a promise of improper benefit: to determine the amount of illegal benefit, to agree on the time and place of the meeting, etc., and in the future to rethink and not take any action to receive it. At the same time, if the fact of accepting them of the promise of unlawful gain will be fixed by law enforcement agencies, means of audio and video control, testimonies of witnesses, etc., in accordance with the provisions of the Criminal Code of Ukraine, he will be prosecuted as an accomplished corrupt crime [17, p. 180].

The third element of the crime, as has already been emphasized, is its subject, that is, a physical, criminal sanity person who committed a crime at the age of which may be criminalized in accordance with the Criminal Code of Ukraine [9]. The subject of the analyzed crimes is not general, but special. He is a person who provides public services. Acording to the criminal law it is a persons whom providing public services calls an auditor, a notary, an appraiser, an authorized person or an official of the Deposit Guarantee Fund, another person who is not a civil servant, an official of local self-government, but carries out professional activities related to providing public services, including services of an expert, arbitration manager, private agent, independent mediator, member of labor arbitration, arbitration judge (when performing these functions), or a state register pa, subject of state registration of rights, public enforcement and private artist. [9] In addition, in view of the fact that medical service is a kind of public service, in our opinion, the legislative list of persons providing public services needs to be supplemented by a private doctor. Of course, a systematic analysis of legislation confirms this thesis, however, taking into account the fundamental nature of the principle of legal certainty for bringing a person to criminal responsibility, the current criminal law requires the above-mentioned additions.

Regarding the essence of the concept of "private doctor", according to the order of the Ministry of Health of Ukraine № 49 of February 2, 2011 "On Approval of Licensing Conditions for Conducting Business Practice for Medical Practice", medical practice is carried out by business entities on the basis of a license provided performance of qualification, organizational, other special requirements established by these License Terms [18]. Qualification requirements for health professionals, regardless of whether they work in state, communal, private health care institutions, are individual entrepreneurs or are independent in their professional activities. Such uniform qualification requirements are set out in the Directory of qualification characteristics of occupations of employees. Issue 78 "Health", approved by the order of the Ministry of Health of Ukraine № 117 of March 29, 2002 [19]. At the same time, the order of the Ministry of Health of Ukraine № 49 of February 2, 2011, "On Approval of Licensing Conditions for conducting economic activities in medical practice" also establishes special requirements for business entities conducting medical practice. In particular, they include: conducting activities in accordance with the information stated in the medical and pharmacy specialties and specialties of junior specialists

in medical and pharmaceutical education; ensuring the accreditation of the health care institution in accordance with the procedure established by the Cabinet of Ministers of Ukraine; compliance with industry standards, health care standards and clinical protocols in the field of health care; compliance with sanitary norms and rules; Gratuitous provision of medical assistance to citizens in accordance with the legislation; observance of labor legislation on acceptance and registration of individuals for work, etc. [18].

The legal status of persons providing medical services is enshrined in a number of legal acts. Thus, it consists of rights and obligations. Seems a fair position A. Bedenko-Sviridchuk that offers all the rights vested in medical professionals, distributed into two groups: universal and professional [20, c. 58]. Human rights are those rights that are characteristic of all workers, regardless of the scope of their constitutional right to work. These rights are enshrined mainly in legal acts of General importance: the Constitution of Ukraine, The labour code of Ukraine, The law of Ukraine "on labour protection", The law of Ukraine "on remuneration of labour". For example, the right to freely choose the place of employment, the right to adequate, safe and healthy working conditions, to wages not lower than those determined by law, legal protection against unlawful dismissal, the right to strike and the like.

Regarding professional rights and freedoms of health care workers, then they, given the analysis of article 77 of the law of Ukraine "fundamentals of legislation of Ukraine on health protection", adapted and detailed to the needs of health workers human rights: the right to education (paragraph "C" of part 1 of article 77) information (n "d" of part 1 of article 77), insurance (paragraph "e" of part 1 of article 77), for social protection (paragraph "e" of part 1 of article 77), for reduced working time (PP. "z" of part 1 of article 77), for a retirement pension (paragraph "and" part 1 of article 77), housing (clause "I", "th" part 1 of article 77),municipality (clause "K" of part 1 of article 77), and others.

With regard to the duties of health workers, the S. Bulets calls them provision of medical care of appropriate quality; informing the patient about the diagnosis, methods of treatment, observance of medical secrecy [21, c. 94]. But P. Koval, A. Projno propose to add to this list the duty to adhere to professional ethics and responsibility procedures for conducting clinical research and application of new methods of prevention, diagnostics, treatment, rehabilitation and medicines that are on the consideration in the established order, but not yet approved for use [22, p. 14]. As for the specific duties of a private doctor, due to his specific status (an individual entrepreneur or a self-employed person), they are set out in the economic, civil and tax legislation. And generally, in our opinion, they can be divided into several groups. First, the obligation to obtain a license to engage in private medical practice, for example, the obligation to comply with the requirements for the premises where such activities will be carried out; the obligation to recruit personnel; the obligation regarding the equipment to be used for the provision of medical services. Second, reporting obligations, both administrative and tax. Third, the obligation to take measures to ensure occupational safety. Fourth, the obligation to ensure the rules for the provision of paid medical services.

The last element of the crime is the subjective side. The subjective, i.e. internal side of corruption crimes, which can be committed by a private doctor, is characterized by direct intent. A subjective side of the wrongful act, the responsibility for the Commission of which is provided for in article 365-2 of the criminal code of Ukraine may be characterized by a mixed form of guilt, i.e. intent regarding the act and negligence with respect to the consequences in the form of significant harm. Obligatory sign of the subjective party of this crime is also a special purpose – obtaining unlawful benefit for themselves or others [14, p. 115].

Regarding the punishment for corruption crimes, in our opinion, the system of penalties for corruption crimes in Ukraine, the subject of which is a private doctor, is quite differentiated. Punishments for them are a fine, deprivation of the right to occupy certain positions or engage in certain activities, public works, correctional work, arrest, confiscation of property, restriction of freedom and imprisonment for a certain period [23, c. 182]. This systematic approach to the development of penalties for corruption crimes is evidence of a comprehensive legislative approach to combating corruption crime and a vivid expression of the principles of individual and objective criminal responsibility.

An analysis of court practice has shown that the commission of a private doctor of corruption crimes is usually accompanied by the commission of other crimes. In particular, forgery of documents, seals, stamps and forms, sale or use of counterfeit documents, seals, stamps (Article 358 of the Criminal Code of Ukraine), an object which, for example, may be a certificate of health, which certifies a certain fact that is capable of cause legal consequences. In addition, a combination of corruption offenses committed by a private doctor, along with the illegal issue of a recipe for the right to acquire narcotic drugs or psychotropic substances (Article 319 of the Criminal Code of Ukraine) is quite widespread. Register of Judicial Decisions of Ukraine contains more than 200 judgment on the conviction of private doctors in the aggregate of crimes, the responsibility for the committing of which is stipulated in Part 1 of Art. 368-4 and Part 1 of Art. 319 of the Criminal Code of Ukraine. In particular, the verdict of the Trinity District Court of the Luhansk Oblast approved an agreement on the recognition of the guilt of a citizen P, who was a doctor of a psychiatrist at a private medical clinic. Thus, a citizen, guided by an mercenary motive (gaining an unlawful benefit), wrote a recipe for a psychotropic medical preparation, "Fenazepam", to a person who had no medical indications for his admission [24].

CONCLUSIONS

In practice, to bring a private doctor to responsibility for committing corruption is extremely difficult, since: firstly, the criminalization of corruption crimes of such persons

took place relatively recently, therefore, pre-trial investigation bodies have not yet set up a well-established system of tactical and methodological actions that would simplify this process Secondly, these crimes are characterized by a high degree of latency, because they are beneficial to both parties: and to a private doctor who may receive unlawful benefits for acts both legal and illegal, and also to the person who proposes, promises or provides such unlawful the benefit of a private doctor's actions or inactivity with the use of the powers granted to him in the interests of the person who offers, promises, or benefits such benefits, or in the interests of a third party. At the same time, it should be noted that the criminalization of the corruption actions of private doctors is an important and significant step aimed not only at combating corruption, but also crime in the area of the circulation of narcotic substances, their analogues and precursors, as well as crimes that encroach on the normal activities of state bodies authorities, local self-government bodies, public organizations, enterprises, institutions and organizations of all forms of ownership.

REFERENCES

1. Corruption perception sindex 2017: http://www.transparency.org/news/feature/corruption_perceptions_index_2017
2. Verkhovna Rada Ukrainy (28, cher. 1996). Konstytutsiya Ukrayiny № 254k/96-VR.: http://zakon3.rada.gov.ua/laws/show/254%D0%BA/96-%D0%B2%D1%80
3. Verkhovna RadaUkrainy (25, kvit. 1995).Zakon № 108/95-vr «Prooplatupratsi».: http://zakon2.rada.gov.ua/laws/show/108/95-%D0%B2%D1%80
4. Zakharchuk O. Z. Normatyvne zakriplennya koruptsiynykh zlochyniv za zakonodavstvom Ukrayiny ta yi khklasyfikatsiya.Visnyk Natsional'noho universytetu «L'vivs'kapolitekhnika». Seriya: Yurydychninauky : zbirnyknaukovykhprats'. 2015; 813:33–38.
5. Khavronyuk M. I. Naukovo-praktychnyy komentar do Zakonu Ukrayiny «Pro zasady zapobihannya i protydiyi koruptsiyi. K. : Atika., 2011. 424 s.
6. Azarov D. S., Hryshchuk V. K., Savchenko A. V. Naukovo-praktychnyy komentar Kryminal'noho kodeksu Ukrayiny. K. : YurinkomInter, 2017. 1104 s.
7. Verkhovna Rada Ukrainy (19, lys. 1992). Zakon № 2801-12 «Osnovy zakonodavstva pro okhoronu zdorov"ya».:http://zakon3.rada.gov.ua/laws/show/2801-12
8. Verkhovna Rada Ukrainy (02, hrud. 2010). PodatkovyykodeksUkrayiny № 2755-VI.: http://zakon5.rada.gov.ua/laws/show/2755-17
9. Verkhovna Rada Ukrainy (05, kvit. 2001). Kryminal'nyy kodeks Ukrayiny №2341-III.: http://zakon5.rada.gov.ua/laws/show/2341-14
10. Sluts'ka T. I. Kryminal'na vidpovidal'nist' za perevyshchennya vlady abosluzhbovykh povnovazhen' :avtoref. dys. nazdobuttyanauk. stupenyakand. yuryd. nauk : 12.00.08 «Kryminal'ne pravo ta kryminolohiya; kryminal'no-vykonavche pravo». K., 2010. 20 s.
11. Bondarenko O. S. Predmet zlochyniv u sferi sluzhbovoyi diyal'nosti ta profesiynoyi diyal'nosti, pov"yazanoyi z nadannyam publichnykh posluh: avtoref. dys. Na zdobuttyan auk. stupenyakand. yuryd. nauk : 12.00.08 «Kryminal'ne pravo ta kryminolohiya; kryminal'no-vykonavche pravo». K., 2016. 20 s.
12. Ryabenko M. V. Zlovzhyvannya povnovazhennyamy audytora u skladi zlochynu, peredbachenomu statteyu 365-2 Kryminal'noho kodeksu Ukrayiny. Chasopys Kyyivs'koho universytetu prava. 2014;1:307–310.
13. Lyubchenko P. M. YU. M. Berezdets'kyy. Orhanizatsiyno-hospodars'ki povnovazhennya: problemy teoriyi i praktyky. Naukovyy visnyk mizhnarodnoho humanitarnoho universytetu. Ser. : Yurysprudentsiya. 2013; 2: 28–31.
14. Savchenko A. V. Koruptsiynizlochyny (kryminal'no-pravovakharakterystyka). K. : «Tsentruchbovoyiliteratury», 2016, 168 s.
15. Shumeyko D. O. Pryynyattya propozytsiyi, obitsyanky abo oderzhannya nepravomirnoyi vyhody sluzhbovoyu osoboyu: problemy pravovoyi kvalifikatsiyi. Yurydychnyy chasopys Natsional'noyi akademiyi vnutrishnikh sprav. 2015; 1: 39–51.
16. Hrodets'kyy YU. V. HizymchukV. S. Zlochyny u sferi sluzhbovoyi diyal'nosti ta profesiynoyi diyal'nosti, pov"yazanoyi z nadannyam publichnykh posluh :navch.-prakt. posib. KH. : Pravo, 2014. 232 s.
17. Zhelik M. Spivvidnoshennya ponyat' «pryynyattya propozytsiyi» ta «pryynyattya obitsyanky» za kryminal'nym pravom Ukrayiny. Pidpryyemnytstvo, hospodarstvo i pravo. 2017; 9: 179–182.
18. Postanova Kabinetu Ministriv Ukrayinyvid 02 ber. 2016 r. № 285 «Pro zatverdzhennya Litsenziynykh umov provadzhennya hospodars'koyi diyal'nosti z medychnoyi praktyky»: http://zakon3.rada.gov.ua/laws/show/285-2016-%D0%BF
19. Nakaz Ministerstva okhorony zdorov"yavid 29 ber. 2002 r. № 117 «Dovidnykkva lifikatsiyny khkharakterystyk profesiy pratsivnykiv. Vypusk 78 «Okhorona zdorov"ya»:http://old.moz.gov.ua/ua/portal/dn_20020329_117.html
20. Bedenko-Zvarydchuk O. Pravovyy status medychnoho pratsivnyka v Ukrayini Praktyka upravlinnya medychnym zakladom. 2012; 3: 57–66.
21. Buletsa S. B. Tsyvil'ni pravovidnosyny, shcho vynykayut' u sferi zdiysnennya medychnoyi diyal'nosti: teoretychni ta praktychni problemy :avtoref. dys. Na zdobuttya nauk. Stupenya dok. yuryd. nauk : 12.00.03 «Tsyvil'ne pravo I tsyvil'nyy protses; simeyne pravo; mizhnarodne pryvatne pravo». Odesa., 2016. 40 s.
22. Koval' P. B., Prokhno O. I. Yurydychni aspekty spivpratsi likarya i patsiyenta (ohlyadzakonodavchoyi bazy). Neonatolohiya, khirurhiya ta perynatal'na medytsyna. 2015; 2 (15): 11–15.
23. Bondarenko O. S . Poka rannya za koruptsiyni zlochyny: komparatyvis'ke doslidzhennya. Porivnyal'no-analitychne pravo. 2017; 3:180–183.
24. Register of Judicial Decisions of Ukraine: http://reyestr.court.gov.ua/Page/1

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Olha S. Bondarenko
Sumy State University, Sumy, Ukraine
tel: + 380662183571
e-mail: olya.tereschenko34@gmail.com

Received: 09.02.2019
Accepted: 12.06.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

MARKERY TOCZNIA UKŁADOWEGO Z OBJAWAMI NEUROPSYCHIATRYCZNYMI I ZABURZENIAMI PSYCHICZNYMI – PRZEGLĄD PIŚMIENNICTWA

SPECIFIC MARKERS OF NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS WITH MENTAL DISORDERS – REVIEW OF THE LITERATURE

Marcin Zarzycki[1], Magdalena Flaga-Łuczkiewicz[2], Joanna Czuwara[1], Lidia Rudnicka[1]
[1]KATEDRA I KLINIKA DERMATOLOGICZNA WARSZAWSKIEGO UNIWERSYTETU MEDYCZNEGO, WARSZAWA, POLSKA
[2]NZOZ CENTRUM TERAPII DIALOG, WARSZAWA, POLSKA

STRESZCZENIE

Toczeń rumieniowaty układowy (SLE – *systemic lupus erythematosus*) jest przewlekłą, autoimmunizacyjną chorobą wielonarządową, znajdującą się w spektrum zainteresowań wielu specjalności. 14–75% pacjentów z SLE ma zaburzenia neuropsychiatryczne. Problematyczna diagnostyka tych schorzeń doprowadziła do powstania prac łączących ich etiologię ze specyficznymi przeciwciałami, zmianami w badaniach obrazowych czy stężeniem katecholamin. Celem pracy jest omówienie częstości występowania zaburzeń neuropsychiatrycznych u pacjentów z SLE oraz potencjalnego związku z zaburzeniami immunologicznymi i markerami chorobowymi. Dotychczasowe piśmiennictwo wskazuje na największą użyteczność markerów serologicznych. Obecność swoistych przeciwciał może pomóc w ukierunkowaniu diagnostyki na zaburzenia psychiatryczne, a w szczególności depresyjne. Badania obrazowe mające ograniczoną użyteczność w rozpoznawaniu zaburzeń psychiatrycznych ułatwiają wykazanie nieprawidłowości natury neurologicznej. Glikokortykosteroidy ze względu na swój wielokierunkowy charakter działania mogą być czynnikami wpływającymi na przebieg chorób neuropsychiatrycznych, zwłaszcza u pacjentów z SLE. Świadomość zaburzeń neuropsychiatrycznych i możliwość ich diagnostyki mają istotne znaczenie w prowadzeniu pacjentów z układowym toczniem rumieniowatym, który istotnie wpływa na jakość ich życia, skuteczność leczenia i psychikę.

SŁOWA KLUCZOWE: toczeń neuropsychiatryczny, autoprzeciwciała, zaburzenia psychiatryczne

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic multiorgan autoimmune disease belonging to spectrum of interest of many medical specialties. Wide range of patients 14–75% with SLE suffers from neuropsychiatric disorders. The problematic diagnosis of neuropsychiatric SLE has generated many studies focusing on etiology of the disease with the presence of specific autoantibodies, abnormalities which can be detected by imaging examinations or correlation with catecholamine levels. The aim of this review paper is to discuss the frequency of neuropsychiatric disturbances in patients with SLE and their potential association with immunological abnormalities and specific disease markers. So far published literature regarding this topic indicates the usefulness of autoantibodies specificity. The use of the specific antibodies may be helpful in targeting diagnostics towards psychiatric disorders, especially depressive ones. Imaging scanning techniques such as computed tomography (CT) have limited value in psychiatric disorders diagnosis but can be useful in neurological symptoms and complains. Therapeutic use of systemic glucocorticosteroids due to anti-inflammatory properties with multidirectional action, may also significantly influence the course of neuropsychiatric diseases, especially in patients with SLE. Awareness of the morbidity of neuropsychiatric disorders and the possibilities of their diagnosis are important in the management of patients with systemic lupus erythematosus, which significantly affects the quality of life of patients, treatment efficacy and psyche.

KEY WORDS: neuropsychiatric lupus erythematosus, autoantibodies, cognitive dysfunctions, psychiatric disorders

Wiad Lek 2019, 72, 7, 1359-1363

WSTĘP

Toczeń rumieniowaty układowy (SLE – *systemic lupus erythematosus*) jest przewlekłą autoimmunizacyjną chorobą wielonarządową będącą w spektrum zainteresowań m.in. dermatologów, reumatologów czy neurologów. Według badań epidemiologicznych średnia częstość występowania SLE wynosi 40–55/100 tys. [1]. Występowanie zaburzeń neuropsychiatrycznych u pacjentów z SLE wykazuje szeroką rozpiętość od 14 do 75%, co zapewne wynika z dużej dowolności interpretacji objawów określanych w kryteriach diagnostycznych choroby według *Systemic Lupus International Collaborating Clinics* (2012 r.) jako „zajęcie układu nerwowego (centralnego i obwodowego)" [2, 3]. Pomocna w diagnostyce może być lista najczęściej występujących dolegliwości układu nerwowego w przebiegu tocznia rumieniowatego układowego stworzona w 1999

roku przez *American College of Rheumatology* [4]. Skrypt ten obejmuje następujące choroby i objawy:
- ostry stan splątania,
- zespół Guillaina-Barrégo,
- zaburzenia lękowe,
- aseptyczne zapalenie opon mózgowo-rdzeniowych,
- zespół mózgowo-naczyniowy,
- zaburzenia funkcji poznawczych,
- zespół demielinizacyjny,
- bóle głowy,
- mononeuropatia,
- mielopatia poprzeczna,
- zaburzenia nastroju,
- zaburzenia motoryki,
- miastenia,
- neuropatie nerwów czaszkowych,
- neuropatia autonomiczna,
- pleksopatia,
- uszkodzenie splotów nerwowych,
- zaburzenia psychotyczne,
- drgawki.

Z wymienionych chorób i objawów cztery znajdują się w spektrum zainteresowań psychiatrów: zaburzenia lękowe, zaburzenia funkcji poznawczych, zaburzenia nastroju oraz zaburzenia psychotyczne. Ze względu na specyfikę chorób psychicznych (subtelność symptomów oraz konieczność bliższego poznania pacjenta) wiele przypadków tocznia neuropsychiatrycznego z zaburzeniami psychicznymi pozostaje niezdiagnozowanych. Rozwiązaniem przedstawionego problemu powinny być konsultacje psychiatryczne pacjentów podejrzewanych o rozwój tocznia neuropsychiatrycznego lub wykorzystanie swoistych markerów – biologicznych, immunologicznych czy neuroobrazowych ułatwiających diagnostykę prowadzoną przez lekarzy innych specjalności.

CEL PRACY

Celem pracy jest przegląd dostępnego piśmiennictwa związanego z toczniem neuropsychiatrycznym z zaburzeniami psychicznymi. Autorzy zwrócili szczególną uwagę na prace naukowe dotyczące możliwości użycia specyficznych markerów do postawienia diagnozy tocznia neuropsychiatrycznego.

ROLA PRZECIWCIAŁ W DIAGNOSTYCE DEPRESJI I ZABURZEŃ FUNKCJI POZNAWCZYCH

Występowanie depresji wśród mieszkańców Polski w wieku 18–64 lat określone jest na poziomie 3% [5]. Według badań światowych częstość współwystępowania depresji u osób chorujących na SLE wynosi 30% [6]. Dziesięciokrotnie wyższa chorobowość w populacji klinicznej pacjentów skłoniła badaczy do poszukiwania swoistych markerów depresji występujących w przebiegu tocznia rumieniowatego układowego.

Według klasyfikacji ICD-10, do rozpoznania epizodu depresyjnego należy stwierdzić występowanie przynajmniej dwóch z poniższych objawów w okresie ostatnich dwóch tygodni:
- obniżenie nastroju,
- utrata zainteresowań i zdolności do radowania się (anhedonia),
- zmniejszenie energii prowadzące do wzmożonej męczliwości i zmniejszenia aktywności.

oraz dwóch z następujących [7]:
- osłabienie koncentracji i uwagi,
- niska samoocena i mała wiara w siebie,
- poczucie winy i małej wartości,
- pesymistyczne, czarne widzenie przyszłości,
- myśli i czyny samobójcze,
- zaburzenia snu,
- zmniejszony apetyt.

Popularna teoria immunologiczna wiążąca wzrost poziomu wykładników stanu zapalnego z rozwojem depresji, wydaje się być trudna do weryfikacji w przebiegu przewlekłej choroby autoimmunologicznej jaką jest SLE. Irańscy badacze wykazali istotną statystycznie różnicę w funkcjonowaniu społecznym pacjentów z SLE i pozytywnym wynikiem występowania przeciwciał Smith (*Sm*) w stosunku do grupy kontrolnej złożonej z osób zdrowych [8]. Badanie to jako jedyne wskazuje na korelację z jednym z kryteriów immunologicznych rozpoznania tocznia rumieniowatego układowego. Dobór grupy kontrolnej jest jednak głównym ograniczeniem pracy. Badacze nie sprawdzili, czy miano przeciwciał *Sm* pozwala na określenie wyższego prawdopodobieństwa wystąpienia objawów depresji wśród pacjentów z SLE.

Bardziej eksploatowanym terenem diagnostycznym jest obecność przeciwciał antyrybosomalnych P wśród pacjentów z SLE. Według metaanalizy z 2015 roku istnieje 7 badań dotyczących tych przeciwciał i zaburzeń nastroju [9]. Praca ta dowodzi istotnej statystycznie różnicy pomiędzy grupami kontrolnymi i badanymi. Jeden z analizowanych artykułów wykazał korelację miana przeciwciał ze stopniem nasilenia depresji wśród pacjentów ze świeżo zdiagnozowanym SLE o czasie trwania <2 lat [10]. Obserwacja ta wskazuje na możliwość wpływu przeciwciał antyrybosomalnych P na rozwój depresji we wczesnej fazie choroby. Badanie nieanalizujące pacjentów świeżo zdiagnozowanych nie wykazało różnic w mianie przeciwciał antyrybosomalnych P pomiędzy pacjentami z depresją i bez niej [11]. Prawdopodobnym wyjaśnieniem zaobserwowanych wyników jest pojawienie się dodatkowych czynników wpływających na rozwój zaburzeń psychicznych w późniejszej fazie SLE i względny spadek znaczenia przeciwciał antyrybosomalnych P.

Część badań związanych z wykrywaniem przeciwciał została poświęcona badaniom zaburzeń funkcji poznawczych u pacjentów z autoprzeciwciałami. W opublikowanych pracach wykazano podwyższone miana przeciwciał przeciwjądrowych, przeciw podwójnej nici DNA, antykardiolipinowych oraz limfocytotoksycznych wśród pacjentów z gorszymi wynikami testów oceny funkcji poznawczych [12–14]. Wstępna diagnoza zaburzeń funkcji poznawczych w gabinetach lekarskich jest możliwa u pacjentów z dodatnią

serologią toczniową w oparciu o proste i dostępne narzędzia takie jak *Mini–Mental State Examination* czy test zegara.

BADANIA OBRAZOWE: SPECT, FMRI, CT

Metodą budzącą duże nadzieje w diagnostyce tocznia neuropsychiatrycznego jest tomografia emisyjna pojedynczych fotonów (SPECT). Badanie z 2001 roku wykazało 100% czułość wykrywania zmian w ośrodkowym układzie nerwowym (OUN) wśród pacjentów w populacji pediatrycznej [15]. Patologiczna perfuzja korowa wykryta w cytowanej pracy była powiązana z zaburzeniami nastroju i świadomości. Powtórzone po kilku miesiącach obrazowania uwidoczniły poprawę perfuzji u 30% pacjentów leczonych sterydami, cyklofosfamidem oraz lekami psychiatrycznymi. Opublikowany w 2015 roku opis 35-letniej kobiety z epizodem maniakalnym w przebiegu SLE wykazał poprawę przepływu mózgowego w badaniu SPECT po wdrożeniu terapii z użyciem steroidów i leku przeciw psychotycznego, arypiprazolu [16]. Taka dynamika zmian nie jest jednak specyficzna dla pacjentów z toczniem neuropsychiatrycznych, a dostępność metody obrazowania może być istotnym czynnikiem ograniczającym. W pracy z 2012 roku wykazano również, że jedynie dwóch z 19 pacjentów z SLE miało zaburzone wyniki SPECT, natomiast 53% badanych z normalnym obrazem OUN uzyskało wyniki testów diagnostycznych wskazujące na zaburzenia poznawcze [12].

Funkcjonalny rezonans magnetyczny (fMRI) znalazł bardzo ograniczone zastosowanie w badaniach chorych na SLE. Jedna opublikowana praca porównywała wyniki pacjentów z zaburzeniami poznawczymi w stosunku do osób zdrowych [17]. Badanie to przeprowadzono w populacji pediatrycznej. Wyniki ujawniły wzrost neuronalnego metabolizmu w grupie badawczej podczas zadań oceniających pamięć roboczą oraz analizy doznań wzrokowych w regionie skroniowym i potylicznym mózgu. W tych miejscach wykryto zmiany przepływu mózgowego przy użyciu metody SPECT [18, 19].

Najbardziej rozpowszechnionym badaniem obrazowania OUN jest tomografia komputerowa (CT). Jej dostępność oraz szybkość wykonania sprawiają, że potencjalne różnice wykryte za jej pomocą mogą być najbardziej przydatne dla lekarzy nie-psychiatrów. Pierwsza praca oceniająca możliwość użycia CT powstała w 1994 roku [20]. Przy użyciu amerykańskiej klasyfikacji chorób psychicznych DSM-III-R z grupy badawczej wydzielono chorych z tzw. dużą depresją odpowiadającą epizodowi depresyjnemu w klasyfikacji międzynarodowej ICD-10. Pacjenci ci wykazali statystycznie istotne różnice w stosunku do grupy kontrolnej złożonej z osób chorych na SLE bez obciążeń psychiatrycznych. Wyniki wskazały na wzrost kalcyfikacji struktur mózgowych oraz poszerzenie systemu komorowego. Dodatkowo przeprowadzone badanie oftalmoskopowe wykazało częstsze patologie naczyniowe oka w grupie pacjentów z dużą depresją.

ZMIANY NACZYNIOWE OUN – CZUŁE, LECZ NIESPECYFICZNE

Toczeń rumieniowaty układowy, który należy do chorób kompleksów immunologicznych, wiąże się także ze wzrostem częstości występowania chorób układu krążeniowo-naczyniowego. W badaniu Greco i wsp. z 2012 roku wykazano korelację między stopniem zwapnienia naczyń krwionośnych i ilością blaszek miażdżycowych a częstością występowania depresji wśród pacjentów z SLE [21]. Związek taki umożliwiałby wytypowanie osób o podwyższonym ryzyku rozwoju depresji w czuły, lecz bardzo niespecyficzny sposób.

NEUROTROFICZNY CZYNNIK POCHODZENIA MÓZGOWEGO (BDNF) – MARKER PROGNOSTYCZNY POPRAWY STANU KLINICZNEGO

Odkryty w 1982 roku neurotroficzny czynnik pochodzenia mózgowego (ang. BDNF – *brain-derived neurotrophic factor*) jest neurotrofiną związaną z neuroplastycznością i regeneracją neuronalną [22]. Odpowiada za przeżycie, wzrost i funkcjonowanie neuronów, a także reguluje układ immunologiczny [23, 24]. W oparciu o jego właściwości powstała hipoteza, że BDNF może być markerem zmian w OUN oznaczanym w krwi krążącej. W 2006 roku został opublikowany przypadek kliniczny 20-letniej pacjentki w stanie majaczenia z 3-miesięczną diagnozą tocznia układowego rumieniowatego [25]. Uwidoczniono strukturalne i metaboliczne zaburzenia OUN podczas obrazowania przy użyciu MRI oraz SPECT, a także wykazano zmiany stężenia BDNF w przebiegu objawów psychotycznych. Obserwacje te zostały rozszerzone o pracę oryginalną opublikowaną w roku 2010 [26]. Stwierdzono w niej podwyższone stężenia BDNF w grupie pacjentów z SLE i objawami psychicznymi, takimi jak: ostry stan splątania, zaburzenia lękowe, zaburzenia nastroju, psychoza, zaburzenia poznawcze. Miano BDNF uległo obniżeniu podczas poprawy stanu klinicznego pacjentów leczonych steroidami systemowymi, cyklofosfamidem oraz lekami psychiatrycznymi. W pracy z 2014 roku wykazano jednak wzrost stężenia BDNF wśród pacjentów z toczniem neuropsychiatrycznym w fazie remisji, ale także wśród chorych z izolowanym SLE w okresie bezobjawowym [27]. Uzyskane dane wskazują, że podwyższone miana BDNF mają znaczenie prognostyczne dla poprawy i nie zależą od manifestacji neuropsychiatrycznej tocznia rumieniowatego układowego.

KATECHOLAMINY – BRAK UŻYTECZNOŚCI KLINICZNEJ

W cytowanym wcześniej przypadku klinicznym analizie poddano również metabolity katecholamin [25]. Badacze wykazali wzrost poziomu kwasu homowanilinowego (HVA) oraz 3-metoksy-4-hydroksyfenyloglicerolu (MHPG) w próbkach krwi pobranych podczas epizodu majaczenia u pacjentki w przebiegu SLE. Wymienione wartości uległy normalizacji po wdrożeniu leczenia lekiem przeciw psychotycznym II generacji, risperidonem. Rozwinięciem tych obserwacji było badanie opublikowane w 2013 roku [28]. Miana MHPG przed wdrożeniem leczenia były podwyższone w grupie pacjentów z SLE w porównaniu do grupy osób zdrowych. Cztery tygodnie po wdrożeniu

Tabela 1. Podsumowanie najważniejszych markerów diagnostycznych tocznia neuropsychiatrycznego.

	Marker	Badania	Ocena
Przeciwciała	Przeciwciała Smith (Sm)	Shakeri i wsp. [8]	Funkcjonowanie społeczne w skali jakości życia uwarunkowanej stanem zdrowia (HRQoL)
	Przeciwciała anty-rybosomalne P	Ho i wsp. [9] Karimifar i wsp. [10] Bai i wsp. [11]	Zaburzenia nastroju (depresja), zwłaszcza w populacji świeżo zdiagnozowanej (<2 lata)
	Przeciwciała przeciwjądrowe, przeciw podwójnej nici DNA, antykardiolipinowe oraz limfocytotoksyczne	Peretti i wsp. [12] Denburg i wsp. 1997 [13] Denburg i wsp. 1988 [14]	Zaburzenia poznawcze
Obrazowanie	Tomografia emisyjna pojedynczych fotonów (SPECT)	Peretti i wsp. [12] Turkell i wsp. [15] Hirachi i wsp. [16] Shen i wsp. [18] Giovacchini i wsp. [19]	Zaburzenia: nastroju, świadomości, poznawcze Odpowiedź na leczenie SLE
	Funkcjonalny rezonans magnetyczny (fMRI)	Barraclough i wsp. [17]	Zaburzenia poznawcze
	Tomografia komputerowa (CT)	Miguel i wsp. [20]	Zaburzenia nastroju (depresja)

leczenia (steroidy systemowe, cyklofosfamid oraz leki przeciwpsychotyczne) badacze nie zauważyli zmian w stężeniach MHPG i HVA. Nie wykazano użyteczności oznaczania metabolitów katecholamin w diagnostyce zaburzeń psychicznych w przebiegu tocznia neuropsychiatrycznego.

CZYNNIKI MODYFIKUJĄCE PRZEBIEG ZABURZEŃ PSYCHICZNYCH

Stosowanie glikokortykosteroidów systemowych (GKS) w terapii tocznia układowego rumieniowatego, pomimo poprawy ogólnoustrojowej i złagodzenia objawów choroby, może skutkować wystąpieniem zaburzeń psychicznych. Częstość występowania objawów neuropsychiatrycznych wywołanych GKS, określanych z ang. *post-steroid neuropsychiatric disease* (PSNP) jest zdecydowanie wyższa w populacji chorych z SLE w stosunku do innych chorób autoimmunologicznych (24,7% *v.* 7,4%) [29]. PSNP został zdefiniowany jako stan związany z przyjmowaniem wysokich dawek steroidów powodujący zaburzenia nastroju, zachowania, funkcji poznawczych, świadomości oraz epizody psychotyczne. W przebiegu tego schorzenia istotnie statystycznie częściej występują zaburzenia nastroju niż w toczniu neuropsychiatrycznym *de novo* (47,2% *vs.* 20,9%). Po wdrożeniu terapii immunosupresyjnej złożonej z pulsów metyloprednizolonu, zastosowaniu cyklosporyny A, cyklofosfamidu, azatiopryny, takrolimusu, metotreksatu, mykofenolanu mofetilu i rytuksymabu oraz leków psychiatrycznych wykazano lepszą poprawę w grupie z PSNP niż z toczniem neuropsychiatrycznym *de novo*. Czynnikiem wpływającym na wystąpienie wspominanych zaburzeń może być uszkodzenie bariery krew-mózg [30]. Rola GKS w indukowaniu objawów psychicznych nie jest jednoznaczna, na co wskazuje badanie z 1994 roku [31]. Wykazano w nim pozytywny wpływ prednizonu na funkcje poznawcze oraz nastrój w populacji chorych z SLE. Ze względu na wielokierunkowość działania GKS, wymagane są dalsze badania w celu określenia ich wpływu na objawy psychiatryczne.

Teoria związania z wpływem ośrodkowych receptorów mózgowych kwasu N-metylo-D-asparaginowego (NMDA) na rozwój tocznia neuropsychiatrycznego doprowadziła do przeprowadzenia badania sprawdzającego efekt podania memantyny (niekompetytywny antagonista NMDA) na mózg myszy laboratoryjnych [32]. Uzyskane wyniki wskazują na możliwość modyfikacji kaskady mediowanej przez wyżej wymieniony czynnik w patogenezie zaburzeń psychicznych w populacji osób chorych na SLE.

WNIOSKI

Brak swoistego markera zmian psychiatrycznych w populacji pacjentów z SLE utrudnia diagnostykę tocznia neuropsychiatrycznego. Ze względu na rozpowszechnienie tych zaburzeń, trudnym do realizacji postulatem wydaje się być kierowanie wszystkich chorych z podejrzeniem współchorobowości na konsultacje psychiatryczne. Przeprowadzony przegląd piśmiennictwa wskazuje na największą wartość diagnostyczną oznaczania poziomu auto-przeciwciał obecnych w SLE, które w pewnym stopniu korelują z objawami psychiatrycznymi (Tab. 1). Nie można natomiast uwzględnić w rutynowych schematach diagnostycznych pozostałych zaprezentowanych w publikacji metod diagnostyki zaburzeń neuropsychiatrycznych ze względu na ograniczenia interpretacji lub dostępności.

Występowanie tocznia neuropsychiatrycznego istotnie przekłada się na rokowanie i skuteczność leczenia tocznia rumieniowatego układowego. Lekarze, niezależnie od dostępnych możliwości diagnostycznych i różnorodnie prezentowanych objawów, powinni być świadomi ryzyka ewolucji SLE do postaci neuropsychiatrycznej.

PIŚMIENNICTWO

1. Owczarek AJ, Michalik R, Kotyla P, Kucharz EJ. Skutki kliniczne, epidemiologiczne i ekonomiczne zmiany kryteriów klasyfikacyjnych wybranych chorób reumatycznych. Reumatologia. 2014;52(2):136-141.
2. Petri M, Orbai AM, Alarcón GS et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64:2677-2686.
3. Jasiewicz A, Samochowiec J. Zaburzenia psychiczne w chorobach tkanki łącznej. Psychiatria. 2011;8(2):39–45.
4. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999;42(4):599-608.
5. Moskalewicz J, Kiejna A, Wojtyniak B. Kondycja psychiczna mieszkańców Polski. Raport z badań „Epidemiologia zaburzeń psychiatrycznych i dostęp do psychiatrycznej opieki zdrowotnej" – EZOP Polska. IPIN, 2013
6. Zhang L, Fu T, Yin R, Zhang Q, Shen B. Prevalence of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. BMC Psychiatry. 2017;17(1):70.
7. Pużyński S, Wciórka J. Klasyfikacja zaburzeń psychicznych i zaburzeń zachowania w ICD-10. Opisy kliniczne i wskazówki diagnostyczne. Kraków: UWM „Vesalius", 2007.
8. Shakeri H, Arman F, Hossieni M, Omrani HR, Vadani A, Shakeri J. Depression, Anxiety and Disease-Related Variables and Quality of Life Among Individuals With Systemic Lupus Erythematosus Living in Kermanshah Province, Iran. Iran Red Crescent Med J. 2015;17(12):e31047.
9. Ho RC, Thaighu C, Ong H et al. A meta-analysis of serum and cerebrospinal fluid autoantibodies in neuropsychiatric systemic lupus erythematosus. Autoimmun Rev. 2015;15(2):124-138.
10. Karimifar M, Sharifi I, Shafiey K. Anti-ribosomal P antibodies related to depression in early clinical course of systemic lupus erythematosus. J Res Med. Sci. 2013;18(10): 860-864.
11. Bai R, Liu S, Zhao Y et al. Depressive and Anxiety Disorders in Systemic Lupus Erythematosus Patients without Major Neuropsychiatric Manifestations. J Immunol Res. 2016;2016:2829018.
12. Peretti CS, Peretti CR, Kozora E, Papathanassiou D, Chouinard VA, Chouinard G. Cognitive Impairment in Systemic Lupus Erythematosus Women with Elevated Autoantibodies and Normal Single Photon Emission Computerized Tomography. Psychother Psychosom. 2012;81:276-285.
13. Denburg SD, Carbotte RM, Ginsberg JS, Denburg JA. The relationship of antiphospholipid antibodies to cognitive function in patients with systemic lupus erythematosus. J Int Neuropsychol Soc. 1997;3:377-386.
14. Denburg SD, Carbotte RM, Long AA, Denburg JA. Neuropsychological Correlates of Serum Lymphocytotoxic Antibodies in Systemic Lupus Erythematosus. Brain Behav Immun. 1988;2:222-234.
15. Turkell SB, Miller JH, Reiff A. Case Series: Neuropsychiatric Symptoms With Pediatric Systemic Lupus Erythematosus. J Am Acad Child Adolesc Psychiatry. 2001;40(4):482-485.
16. Hirachi T, Ishii H, Tada Y, Noguchi T, Haraguchi Y, Tateishi H. Mania occurring during systemic lupus erythematosus relapse and its amelioration on clinical and neuroimaging follow-up. Lupus. 2015;24(9):990-993.
17. Barraclough M, Elliott R, McKie S, Parker B, Bruce IN. Cognitive dysfunction and functional magnetic resonance imaging in systemic lupus erythematosus. Lupus. 2015;24(12):1239-1247.
18. Shen YY, Kao CH, Ho YJ, Lee JK. Regional Cerebral Blood Flow in Patients with Systemic Lupus Erythematosus. J Neuroimaging. 1999;9:160-164.
19. Giovacchini G, Mosca M, Manca G et al. Cerebral Blood Flow in Depressed Patients with Systemic Lupus Erythematosus. J Rheumatol. 2010;37:1844-1851.
20. Miguel EC, Rodrigues Pereira RM, De Braganca Pereira CA et al. Psychiatric manifestations of systemic lupus erythematosus: clinical features, symptoms, and signs of central nervous system activity in 43 patients. Medicine (Baltimore). 1994;73(4):224-232.
21. Greco CM, Li T, Sattar A et al. Association between depression and vascular disease in systemic lupus erythematosus. J Rheumatol. 2012;39(2):262-268.
22. Leibrock J, Lottspeich F, Hohn A i wsp. Molecular cloning and expression of brain-derived neurotrophic factor. Nature. 1989;341:149-152.
23. Lewin GR, Barde YA. Physiology of neurotrophins. Annu Rev Neurosci. 1996;19:289–317.
24. Vega JA, Garcia-Suarez O, Hannestad J, Perez-Perez M, Germana A. Neurotrophins and the immune system. J Anat. 2003;203:1–19.
25. Ikenouchi A, Yoshimura R, Ikemura N, Utsunomiya K, Mitoma M, Nakamura J. Plasma levels of brain derived-neurotrophic factor and catecholamine metabolites are increased during active phase of psychotic symptoms in CNS lupus: a case report. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(7):1359-1363.
26. Ikenouchi-Sugita A, Yoshimura R, Okamoto T et al. Serum brain-derived neurotrophic factor levels as a novel biological marker for the activities of psychiatric symptoms in systemic lupus erythematosus. World J Biol Psychiatry. 2010;11(2):121-128.
27. Tamashiro LF, Oliveira RD, Oliveira R et al. Participation of the neutrophin brain-derived neurotrophic factor in neuropsychiatric systemic lupus erythematosus. Rheumatology (Oxford). 2014;53(12):2182-2190.
28. Ikenouchi-Sugita A, Yoshimura R, Hori H et al. Plasma catecholamine metabolite levels and the activities of psychiatric symptoms in systemic lupus erythematosus. Hum Psychopharmacol. 2013;28(2):198-202.
29. Shimizu Y, Yasuda S, Kako Y et al. Post-steroid neuropsychiatric manifestations are significantly more frequent in SLE compared with other systemic autoimmune diseases and predict better prognosis compared with de novo neuropsychiatric SLE. Autoimmun Rev. 2016;15(8):786-94.
30. Nishimura K, Harigai M, Omori M, Sato E, Hara M. Blood-brain barrier damage as a risk factor for corticosteroid-induced psychiatric disorders in systemic lupus erythematosus. Psychoneuroendocrinology. 2008;33(3):395-403.
31. Denburg SD, Carbotte RM, Denburg JA. Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. Arthritis Rheum. 1994;37(9):1311-1320.
32. Marcinko K, Parsons T, Lerch JP, Sled JG, Sakic B. Effects of prolonged treatment with memantine in the MRL model of CNS lupus. Clin Exp Neuroimmunol. 2012;3(3):116-128.

Konflikt interesów:
Wszyscy autorzy deklarują brak konfliktu intresów.

AUTOR KORESPONDUJĄCY
Joanna Czuwara
Katedra i Klinika Dermatologiczna
Warszawskiego Uniwersytetu Medycznego,
ul. Koszykowa 82a, 02-008 Warszawa, Polska
e-mail: jczuwara@yahoo.com

Nadesłano: 27.12.2018
Zaakceptowano: 15.05.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

METODA REZONANSU STOCHASTYCZNEGO W FIZJOTERAPII – PRZEGLĄD PIŚMIENNICTWA

STOCHASTIC RESONANCE METHOD IN PHYSIOTHERAPY – A REVIEW OF THE LITERATURE

Mateusz Bartczyk[1], Andrzej Suchanowski[2], Marta Woldańska-Okońska[1]
[1]KLINIKA REHABILITACJI I MEDYCYNY FIZYKALNEJ UM, ŁÓDŹ, POLSKA
[2]WYDZIAŁ FIZJOTERAPII OLSZTYŃSKIEJ SZKOŁY WYŻSZEJ IM. J. RUSIECKIEGO, OLSZTYN, POLSKA

STRESZCZENIE

Nieliniowość jest istotną cechą wielu struktur organizmu człowieka, która może wynikać z deterministycznych właściwości organizmu i szumu. Szum definiuje się jako przypadkowe lub nieregularne fluktuacje lub zakłócenia, które nie są częścią sygnału. Rezonans stochastyczny (SR) termin pierwotnie używany w bardzo specyficznym kontekście, jest obecnie szeroko stosowany do opisu dowolnego zjawiska, w którym obecność szumu w systemie nieliniowym jest lepsza dla jakości sygnału wyjściowego niż jego brak. Prowadzone badania na potrzeby fizjoterapii polegają na ocenie odziaływania platformy generującej wymuszone drgania mechaniczne o określonych parametrach w wybranych jednostkach chorobowych, dyscyplinach sportowych, a także profilaktyce. Celem pracy jest omówienie metody rezonansu stochastycznego i analiza wyników najistotniejszych prac omawiających stosowanie oraz efektywność oddziaływania terapeutycznego na organizm człowieka. Stosowanie metody rezonansu stochastycznego wymusza mechaniczne wibracje, które charakteryzują się zmiennością rytmu, amplitudy i kierunku wibracji, co wymusza adaptację posturalną regulowaną przez OUN i odpowiedzi na bodźce zakłócające równowagę ciała. Przeprowadzono analizę efektywności oddziaływania terapeutycznego w zakresie zaburzeń równowagi ciała, reedukacji lokomocji u osób z częściowym uszkodzeniem rdzenia kręgowego, zmienności motoryki oraz zmian stężeń hormonalnych. Terapia rezonansem stochastycznym może powodować zmniejszenie lub usunięcie dysfunkcji w wielu jednostkach chorobowych, jednakże wymagane są kolejne badania oceniające skuteczność stosowanej terapii.

SŁOWA KLUCZOWE: fizjoterapia, rezonans stochastyczny, efekty terapeutyczne

ABSTRACT

Non-linearity is an important feature of many human body structures that may result from deterministic properties of the body and noise. Noise is defined as accidental or irregular fluctuations or disturbances that are not part of the signal. Stochastic resonance (SR), the term originally used in a very specific context, is now widely used to describe any phenomenon in which the presence of noise in a nonlinear system is better for the quality of the output signal than its absence. The conducted research for the needs of physiotherapy consists in assessing the impact of the platform generating forced mechanical vibrations with specific parameters in selected disease entities, sports disciplines, as well as prevention. **The aim** of the work is to discuss the stochastic resonance method and to analyze the results of the most important works discussing the use and effectiveness of therapeutic impact on the human body. The use of the stochastic resonance method enforces mechanical vibrations, which are characterized by the variability of rhythm, amplitude and direction of vibrations, which enforces postural adjustment regulated by the CNS and response to stimuli that disturb the body's balance. The analysis of the effectiveness of therapeutic impact in the field of body balance disorders, reeducation of locomotion in people with partial spinal cord injury, motor motility and changes in hormonal concentrations was carried out. Stochastic resonance therapy can reduce or eliminate dysfunction in many disease entities, however, further studies are needed to assess the effectiveness of the therapy.

KEY WORDS: physiotherapy, stochastic resonanse, therapeutic effects

Wiad Lek 2019, 72, 7, 1364-1370

WSTĘP

Nieliniowość jest istotną cechą wielu struktur organizmu człowieka, która może wynikać z dwóch różnych źródeł. Pierwszym źródłem są deterministyczne właściwości organizmu, natomiast drugim źródłem jest szum. Szum definiuje się jako przypadkowe lub nieregularne fluktuacje lub zakłócenia, które nie są częścią sygnału [1]. Obserwacje losowych fluktuacji mogą świadczyć o źródłowej losowości biologicznej, która mogłaby zostać wykorzystana ze względu na korzyść funkcjonalną, m.in. zjawisko rezonansu stochastycznego. Alternatywnie, pomiary sygnału zawierającego informacje o nieprzewidywalnej zmienności mogą świadczyć o tym, że przypadkowość została już wykorzystana do wspomagania reprezentacji informacji. Rezonans stochastyczny (SR) termin pierwotnie używany w bardzo specyficznym kontekście, jest obecnie szeroko stosowany do opisu dowolnego zjawiska, w którym obecność szumu w systemie nieliniowym jest lepsza dla jakości

sygnału wyjściowego niż jego brak. Zjawisko rezonansu stochastycznego występuje, gdy losowość ma pozytywną rolę w kontekście przetwarzania sygnału [2]. Zaobserwowano losowe fluktuacje na poziomie transmisji sygnałów: bodźców wzrokowych (fotoreceptor i kaskada wzmacniająca sygnał) [3], bramkowania kanałów jonowych [1], transmisji synaptycznej [1], ekspresji genów [4], funkcji serca [5], sieci neuronalnych mózgu [1] i każdego etapu pętli sensomotorycznej, począwszy od postrzegania sygnałów czuciowych po generowanie reakcji motorycznych [6, 7]. Szum ma bezpośrednie konsekwencje behawioralne, od nastawiania progów percepcyjnych po wpływ na precyzję ruchów [1].

Określone dysfunkcje w narządach zmysłów odpowiedzialne za słyszenie, dotyk lub wrażenia wizualne czy układ kontroli równowagi mogą być rezultatem wyższej percepcji sensorycznej w porównaniu do zdrowych osób. Szczególnie godne uwagi są badania, które wykazały, że niski poziom szumu wejściowego dodany do sygnału nośnego (mechaniczny lub elektryczny) może być wykorzystany do wzmocnienia somatosensji i poprawy wydajności kontroli procesów równoważnych. Wyniki uzyskane w badaniu sugerują, że zjawisko rezonansu stochastycznego może mieć wpływ na mechanoreceptory [8, 9]. Zaobserwowano, że szum mechaniczny zastosowany na podeszwową powierzchnię stóp za pomocą wibrujących wkładek do butów mogą poprawić postawę i równowagę u osób po udarze mózgu, z neuropatią cukrzycową lub w podeszłym wieku w wyniku zmniejszenia chwiejności postawy i zachowania równowagi ciała w porównaniu do osób zdrowych w podeszłym wieku lub młodych [10, 11]. Następnym przykładem jest generowanie losowego szumu w implantach ślimakowych, który może prowadzić do poprawy słuchu u osób głęboko niesłyszących przez bezpośrednią elektroniczną stymulację nerwu słuchowego, używając chirurgicznie zaimplementowanego układu elektrod [12, 13]. Kolejnym przykładem jest zastosowanie SR w respiratorach wspomagania życia. W celu dokładniejszego odtworzenia naturalnego oddychania wprowadzono losowy szum do działania wentylatora mechanicznego i stwierdzono, że poprawiał on wydajność struktur organizmu na kilka sposobów [14] . Obecnie są prowadzone badania w zakresie inżynierii biomedycznej w obszarach: interfejsów mózg-maszyna, implanty ślimakowe, implanty z pniem mózgu, implanty siatkówki oka w celu przywrócenia widzenia, co oznacza, że istnieje rosnąca potrzeba zrozumienia, jak nieprzewidywalne fluktuacje mogą być wykorzystywane w medycynie [2].

Celem pracy jest omówienie metody rezonansu stochastycznego i analiza wyników najistotniejszych prac omawiających stosowanie oraz efektywność oddziaływania terapeutycznego na organizm człowieka.

Prowadzone badania na potrzeby fizjoterapii polegają na ocenie odziaływania platformy generującej wymuszone drgania mechaniczne o określonych parametrach w wybranych jednostkach chorobowych, dyscyplinach sportowych, a także profilaktyce [15]. Stosowanie metody rezonansu stochastycznego powoduje mechaniczne wibracje, które charakteryzują się zmiennością rytmu, amplitudy i kierunku wibracji, co wymusza adaptację posturalną regulowaną przez OUN i odpowiedzi na bodźce zakłócające równowagę ciała [16].

W urządzeniu SR-WBV można rozróżnić zakresy częstotliwości theta i alfa. Zakres częstotliwości theta (3.5-7.5 Hz) jest odwzorowaniem ruchów cyklicznych (np. bieganie). Statyczne i dynamiczne skurcze mięśni wykazują wzór działania w zakresie częstotliwości alfa (7,5-12,5 Hz) [16]. Podczas stochastycznej wibracji całego ciała (SR-WBV) pacjent stoi na dwóch płytkach, które poruszają się w sposób niejednorodny i wielopłaszczyznowo (przód/tył, prawo/lewo, w górę/w dół), powodując destabilizację równowagi [17]. Regulacja wibracji odbywa się poprzez wzajemne skurcze koncentryczne i ekscentryczne, co dodatkowo prowadzi do stosunkowo rytmicznych wzorców aktywacji mięśni. Natomiast oscylacje stochastyczne są nieprzewidywalne. W ten sposób stale pojawiają się nowe stany podrażnienia i wymagają ciągłych zmian napięcia w celu wytworzenia aktywacji mięśni dostosowanych do określonego schematu bodźca, aczkolwiek jest to możliwe tylko w ograniczonym zakresie, pomimo korekcji balistycznych [18]. Sytuacje wymagające kontroli motorycznej zawsze zawierają pewną ilość wariancji i niepewności. W związku z tym tylko część wymagań może zostać spełniona przez już istniejące lub wyuczone mechanizmy kontrolne [19]. Pozostały składnik zmienny wymaga oszacowania maksymalnej wiarygodności. Odbywa się to poprzez interpolację i ekstrapolację między znanymi odniesieniami. Podczas gdy stymulacja sinusoidalna zawiera zbędne fragmenty informacji, stymulacja stochastyczna generuje wiele odniesień, które pozwalają na bardziej odpowiednią ocenę sytuacji i związaną z tym kalibrację receptorów wielu narządów [19].

W procesie stymulacji bodźcami wibracyjnymi w sztucznej sieci komórek nerwowych, bodźce drgań stochastycznych wywołują potencjały aktywacji komórek nerwowych w porównaniu do drgań sinusoidalnych, które są podprogowe [19]. Co więcej, badania wykazały, że utrata czucia związana z wiekiem i chorobą może być odwracalna poprzez stosowanie zjawiska rezonansu stochastycznego. W grupie pacjentów w podeszłym wieku, po udarze mózgu oraz z neuropatią cukrzycową zdolność wykrywania sygnałów stochastycznych jest lepsza o 16 do 34% w porównaniu do sygnałów sinusoidalnych [18]. Haas i wsp. w przeprowadzonym badaniu nie wykazali zmian w właściwościach proprioceptywnych po terapii rezonansem stochastycznym u osób z chorobą Parkinsona, która redukuje objawy, a zwłaszcza zaburzenia kontroli postawy. W odniesieniu do ogólnych trudności w ocenie propriocepcji nie można całkowicie wykluczyć zmian proprioceptywnych. Jednak nie pojawiły się żadne dowody ani nawet tendencje do zmian w propriocepcji [20].

Uwalnianie czynników neurotroficznych jest możliwe poprzez stymulację wrzecion nerwowo-mięśniowych, które mają wysoką wrażliwość na bodźce stochastyczne (arytmiczne). Substancje te „odżywiają" komórki nerwowe, odpowiadają za nowe powiązania nerwowe i chronią nerwy przed zanikiem, tworząc potencjał do

lepszej kontroli i leczenia chorób neurodegeneracyjnych, takich jak choroba Parkinsona, stwardnienie rozsiane lub zanikowe stwardnienie boczne (ALS) [19]. Stochastyczne drgania mechaniczne wchodzą w interakcję z równie stochastycznymi parametrami czynnościowymi układu nerwowego [15]. Powodują wyższą aktywność dodatkowej kory ruchowej (SMA – *supplementary motor area*) ważnej dla generowania skomplikowanych wzorców ruchowych, która stanowi ścisłe połączenie z systemem działania dopaminergicznego. Prowadzą do stosunkowo mocnych aktywacji obszarów przedczołowej kory, które są ważne dla nabywania wiedzy (pozyskiwania informacji) [21]. Ponadto, zwiększona aktywność w ciele prążkowym (*striatum*), ułatwia wykonanie ruchów dobrowolnych w sposób płynny i pewny, wybierając odpowiednie dla niego wykonanie i inicjując ruch, jednocześnie zapewniając zahamowanie ruchów opozycyjnych [22]. Zaobserwowano zwiększoną aktywność móżdżku, która zapewnia większą neuroplastyczności i lepsze wyniki rehabilitacji u pacjentów z SM i po udarze mózgu [21].

Następstwem unieruchomienia jest zmniejszenie syntezy białek, przy czym pierwsza zmiana może zostać wykryta już po 5 godzinach, natomiast w okresie bezczynności 7–14 dni zmniejsza się o 50–60%. Zmiany strukturalne i morfologiczne są związane z modyfikacjami biochemicznymi. Przy dostatecznie długim braku aktywności, centralne i obwodowe sieci neuronalne ulegają degeneracji, zmniejszając w sposób zrównoważony możliwości aktywacji mięśniowej. Związana relatywnie duża część szybkich jednostek o wysokim progu aktywacji prowadzi do stanu, w którym mięsień nie jest aktywowany wcale lub aktywowany wyłącznie maksymalnie, a tym samym nie powstaje bodziec do skutecznej reedukacji funkcji mięśni, co wiąże się ze stresem oksydacyjnym i zmniejszoną odpornością na zmęczenie [18]. Bodźce o właściwościach stochastycznych, w porównaniu do sygnałów harmonicznych, mają tę zaletę, generowania niskich natężeń bodźców mechanicznych (niska amplituda względem niskiej częstotliwości) w celu uzyskania odpowiednich efektów czuciowych i nerwowo-mięśniowych bez ryzyka uszkodzenia struktur organizmu pacjenta czy zablokowania aktywności mięśni. W rezultacie, drgania stochastyczne stanowią optymalny bodziec dla osób w podeszłym wieku, pacjentów z wyraźnymi zaburzeniami ruchowymi, a nawet po dłuższym okresie bezczynności motorycznej [23].

Wskazania do stosowania metody rezonansu stochastycznego są opracowane przez producentów urządzeń oraz fizjoterapeutów i obejmują: udar mózgu lub uraz czaszkowo-mózgowy (niedowład), chorobę Parkinsona, stwardnienie rozsiane i zanikowym stwardnieniu bocznym, uraz rdzenia kręgowego, urazy ortopedyczne, alloplastyka stawów biodrowych lub kolanowych, neuropatia/cukrzyca, osteoporoza, zaburzenia równowagi (ataksja), nietrzymanie moczu, depresja, nadpobudliwość psychoruchowa, autyzm, mózgowe porażenie dziecięce. Natomiast do przeciwwskazań należą: rana pooperacyjna, ostre stany zapalne (zależy od objętej struktury względem lokalizacji stanu zapalnego), wypuklina krążka międzykręgowego (zależy od stopnia wypukliny, wystąpienia deficytów neurologicznych, względne przeciwwskazanie), spondyloza, kamica nerkowa lub żółciowa, zaawansowana osteoporoza z ostrym ryzykiem złamań, schizofrenia, padaczka, drgawki, zaburzenia spostrzegania i zawroty głowy, implant (elektroniczny serca, rogówki oka, ślimakowy), głęboka stymulacja mózgu w chorobie Parkinsona (zalecane badanie lekarskie, względne przeciwwskazanie), znaczne nadciśnienie lub hipotonia, zaburzenia rytmu serca, tętniaki, zakrzepica kończyn dolnych, nudności, złe samopoczucie, migrena, nowotwory, ciąża [24]. Zaleca się ostrożną ocenę historii medycznej pacjenta przed stymulacją wibracjami całego ciała w celu oceny przeciwwskazań lub potencjalnego ryzyka. Stosowanie wibracji całego ciała może powodować działania niepożądane, tj.: mrowienie lub miejscowe zaczerwienienie skóry kończyn dolnych, bolesność mięśni, zmęczenie oraz łagodne zawroty głowy, aczkolwiek występowanie objawów jest rzadkie [25].

ZABURZENIA RÓWNOWAGI CIAŁA

Suchanowski i Bartczyk zastosowali 15 zabiegów drgań stochastycznych (3 i 6 Hz, poziom szumu 3, 5 serii po 60 s., oddzielone przerwami po 60 s., 3x/tydzień w ciągu 5 tyg.) u 3 osób po udarze mózgu w stadium przewlekłym choroby. Nie dokonano analizy statystycznej ze względu na małą liczebność grupy. Zaobserwowali poprawę w teście „Wstań i Idź" o 17 do 21%, w teście „Sięgania" o 33 do 100% oraz w teście „30 second Stand Chair" o 16 do 37%, aczkolwiek uzyskany rezultat świadczy o wysokim ryzyku upadków. Na potrzeby kontroli postępowania fizjoterapeutycznego przeprowadzono pomiar ciśnienia tętniczego krwi (BP) i częstości skurczów serca (HR). Odnotowano obniżone wartości BP i HR w ciągu kolejnych serii w porównaniu do wartości spoczynkowych [26].

Bartczyk i wsp. ocenili efekty drgań stochastycznych w zakresie równowagi statycznej u osób ze stwardnieniem rozsianym. 27 osób o umiarkowanej niepełnosprawności (skala EDSS 2,5-5) zostały podzielone losowo na grupę eksperymentalną i kontrolną. W grupie eksperymentalnej zastosowano indywidualne postępowanie usprawniające o czasie 770,4±76,2 min (wartość średnia w ciągu tyg.) w uzupełnieniu z 10 zabiegami rezonansu stochastycznego (3 i 6 Hz, poziom szumu 3) w 5 seriach po 1 min, oddzielone przerwami o tym samym czasie. W grupie kontrolnej zastosowano indywidualne postępowanie usprawniające o czasie 715,1±95,3 min (wartość średnia w ciągu tyg.). Ocena stabilności postawy ciała została przeprowadzona na stabilnym podłożu za pomocą platformy Biodex Balance System SD w zakresie ogólnego wskaźnika stabilności, wskaźnika stabilności A/P, wskaźnika stabilności M/L, odsetka [%] czasu wychyleń w strefie A, B, C, D oraz odsetka [%] czasu wychyleń w kwadrantach I, II, III, IV. W grupie eksperymentalnej ogólny wskaźnik stabilności zmniejszył się z 1,2° do 0,7° (p=0,095), co więcej średnia wartość wskaźnika stabilności A/P uległa poprawie z 0,9° do 0,5° (p=0,051). Średnia wartość procentowa czasu wychyleń w strefie B uległa zmniejszeniu z 2,7 do 0,2% (p=0,053) po zastosowaniu

10 zabiegów rezonansem stochastycznym. W grupie kontrolnej odnotowano zmniejszenie średniej wartości wskaźnika stabilności A/P z 0,9° do 0,5° (p=0,080) między pierwszym a drugim tygodniem stosowanej terapii [27].

Rogan i wsp. przeprowadzili badanie skrzyżowane u osób starszych nieuprawiających aktywności fizycznej w zakresie równowagi statycznej i dynamicznej oraz czasu reakcji psychomotorycznej. Dokonano oceny za pomocą testu: *Semi-Tandem Stand*, Sięgania, Wstań i Idź, czasu reakcji psychomotorycznej dłoni i stóp oraz oceny prędkości lokomocji podczas pojedynczego lub podwójnego zadania. 20 osób podzielono na grupę A (5 Hz, poziom szumu 4 / 1 Hz, poziom szumu 1) i grupę B (1 Hz, poziom szumu 1 / 5 Hz, poziom szumu 4). Zastosowano 5 serii po 60 s, oddzielone przerwami o tym samym czasie 3 razy w tygodniu w ciągu 4 tygodni. Po 12 dniach zabiegowych zastosowano 16 dni odpoczynku, a następnie uczestnicy byli poddani 12 zabiegom o przeciwnych parametrach stymulacji. Zaobserwowano zmniejszenie czasu przejścia dystansu 20 m w teście Wstań i Idź, aczkolwiek uzyskany rezultat nie był statystycznie istotny (p=0,097) [28].

Srokowski i wsp. ocenili skuteczność 10 zabiegów rezonansem stochastycznym (8 serii po 60 s, oddzielone przerwami o tym samym czasie, 5x/tydzień) u dzieci z mózgowym porażeniem dziecięcym w zakresie równowagi statycznej i dynamicznej. Dokonano oceny za pomocą testu Wstań i Idź, próby Romberga (otwarte i zamknięte oczy) oraz skali Tinetti. Zaobserwowano zmniejszenie czasu przebytego dystansu w teście Wstań i Idź o 22%, na podstawie skali Tinetii odnotowano poprawę o 2,3±2,0 pkt (ok. 30%), w próbie Romberga uzyskano lepszy rezultat przy otwartych i zamkniętych oczach odpowiednio o 6±6,8 s i 6,4± 5,8 s Uzyskana poprawa wyników była statystycznie istotna (p<0,001) [29].

Rogan i wsp. opracowali metaanalizę dotyczącą wpływu stochastycznej wibracji całego ciała u osób z zaburzeniami równowagi i historii upadków. W celu poprawy równowagi statycznej i dynamicznej u osób z schorzeniami neurodegeneracyjnymi należy stosować 3x w tygodniu z częstotliwością 3–6 Hz w 5 seriach po 60 s., oddzielonymi przerwami o tym samym czasie, natomiast stosowanie terapii w ciągu 4 tygodni powoduje poprawę mobilności u osób w podeszłym wieku [30].

Elfering i wsp. zastosowali drgania stochastyczne (4–8 Hz, 3 serie po 60 s, oddzielone przerwami o tym samym czasie, 3x/tydzień w ciągu 4 tyg.) u inżynierów branży produkcji systemów lotniczych. Zaobserwowano zwiększoną kontrolę zachowania balansu ciała (p<0,05) oraz znaczą redukcję bólu w odcinku lędźwiowym kręgosłupa o charakterze mięśniowo-szkieletowym (p<0,05) u osób zgłaszających dolegliwości bólowe dolnej części tułowia w ciągu 4 tygodni przed rozpoczęciem badania [31].

USZKODZENIE RDZENIA KRĘGOWEGO

Haas i wsp. ocenili skuteczność drgań stochastycznych u osób z paraplegią i tetraplegią w następstwie częściowego uszkodzeniem rdzenia kręgowego (URK). W grupie kontrolnej i eksperymentalnej zastosowano środki fizjoterapeutyczne uwzględniając reedukację lokomocji, ponadto, w grupie eksperymentalnej uzupełniono postępowanie usprawniające o zastosowanie drgań stochastycznych (4–6 Hz, 5 serii po 60 s, oddzielone przerwami o tym samym czasie). Dokonano oceny w zakresie przebytego dystansu w ciągu 2 min oraz utrzymania pozycji stojącej przez jak najdłuższy czas (bez pomocy pacjentowi) co 18-21 dni. Czas trwania terapii wyniósł około 60 dni. Odnotowano poprawę parametrów docelowych w obu grupach, jednakże zaobserwowano statystycznie istotne różnice w grupie eksperymentalnej odpowiednio o 47% i 31% w porównaniu do grupy kontrolnej [32]

Jednym z celów fizjoterapii u pacjentów z paraplegią jest reedukacja lokomocji. Zaburzenia lokomocji z jednej strony są skompensowane zmniejszeniem masy ciała, a z drugiej strony, wymaganą interwencji fizjoterapeutów lub dedykowanych urządzeń, takich jak bieżnia ruchoma lub Lokomat. Chociaż mechanizmy neuronalne są słabo poznane, główne znaczenie ma aktywacja zespołu komórek CPG (*central pattern generator*) powodując rytmiczną i naprzemienną aktywację mięśni nóg, a tym samym wspomaga lokomocję. Aktywacja CPG w stanie fizjologicznym odbywa się przez stymulowanie ośrodków nadrdzeniowych w następstwie aplikacji drgań mechanicznych, co może być stosowane w urazie rdzenia kręgowego (URK). W szczególności centralną rolę odgrywa powtarzająca się reakcja odruchowa. Ta funkcjonalność opiera się na różnych założeniach. Tak więc istnieje silna korelacja pomiędzy zdolnością ruchową a funkcją odruchu wyzwalaną przez stymulację proprioceptywną lub eksteroceptywną. Inne prace dowodzą, że reedukacja lokomocji wiąże się ze wzrostem zdolności przetwarzania sygnału aferentnego. Uważa się również, że receptory, a szczególności włókna dośrodkowe typu Ia i II, sprzyja wzrostowi komórek nerwowych i pojawieniu się nowych połączeń neuronalnych [23]

ZMIENNOŚĆ MOTORYKI CZŁOWIEKA

Rogan i wsp. wyjaśniają, że stosowanie drgań stochastycznych jest korzystne na początkowym etapie usprawniania u osób nieaktywnych fizycznie lub osób w podeszłym wieku ze względu na układ nerwowo-mięśniowy, który może nie być wstanie zrealizować wyższych obciążeń treningowych. Wzrost zdolności wytrzymałości siłowej po stymulacji bodźcami wibracyjnymi w krótkim czasie wiąże się ze skuteczniejszą koordynacją nerwowo-mięśniową w postaci bardziej zsynchronizowanej aktywności mięśniowej i większej liczby rekrutowanych jednostek ruchowych. Co więcej, stosowanie stochastycznej wibracji u osób poruszających się samodzielnie lub z pomocą lokomocyjną stanowi uzupełnienie programu usprawniania wśród wielu środków terapeutycznych [33].

Rogan i wsp. przeprowadzili randomizowane badanie stosując drgania stochastyczne uzupełnione taneczną grą wideo u osób w podeszłym wieku. Dokonano oceny w zakresie sprawności fizycznej za pomocą testu Short Physical Performance Battery (SPPB), maksymalnego dowol-

nego skurczu izometrycznego (IMVC) i siły eksplozywnej (wskaźnik IRFD: *isometric rate of force development*, N/ms) zginaczy i prostowników stawu kolanowego. Osobom w grupie eksperymentalnej zastosowano częstotliwość 3–6 Hz z poziomem szumu 4 w 5 seriach po 60 s, oddzielone przerwami o tym samym czasie (3x/tydzień przez 8 tygodni), w 5-8 tygodniu drgania stochastyczne zostały uzupełnione taneczną grą wideo (3x/tydzień). W grupie kontrolnej zastosowano częstotliwość 1 Hz z poziomem szumu 1 w 5 seriach po 60 s., oddzielone przerwami o tym samym czasie (3x/tydzień przez 8 tygodni), w 5–8 tygodniu drgania stochastyczne zostały uzupełnione ćwiczeniami dynamicznymi kończyn dolnych na trampolinie (3x/tydzień). W grupie eksperymentalnej na podstawie SPPB zaobserwowano statystycznie istotne różniące po 4 (p=0,01) i 8 (p=0,004) tygodniach terapii. Po 8 tygodniach zaobserwowano znacznie istotny wzrost IMVC zginaczy lewej kończyny (p=0,03). Statystycznie istotne różnice wskaźnika IRFD zginaczy i prostowników stawów kolanowych między grupami zaobserwowano po 4 tygodniach (p<0,05) i 8 tygodniach (p<0,05) w poszczególnych przedziałach czasowych 0–30, 0–50, 0–100, 100–200 ms w porównaniu do grupy kontrolnej [34].

W kolejnym badaniu Elfering i wsp. oceniali wpływ drgań stochastycznych u 23 studentek w celu zidentyfikowania możliwych wyjaśnień dotyczących działań profilaktyki na zaburzenia mięśniowo-szkieletowe. Dokonano oceny aktywności mięśnia czworobocznego, zmienności częstości skurczów serca, właściwości tkanki skórnej (temperatura, zaczerwienienie, przepływ krwi) oraz kwestionariuszy samoopisowych oceny bólu przewlekłego i stanu mięśni (samopoczucie i relaks). W grupie eksperymentalnej zastosowano częstotliwość 6 Hz (poziom szumu 4), natomiast w grupie kontrolnej 2 Hz (poziom szumu 0). W grupie eksperymentalnej wzrosła aktywność mięśnia czworobocznego średnio o 3,47% (p=0,006) w porównaniu do grupy kontrolnej [18]. Na podstawie wielkości przepływu krwi – perfuzji (PU – *perfusion unit*), tylko w rejonie odcinka środkowego tułowia wykazano statystycznie istotne zmiany (p<0,0005). W grupie kontrolnej odnotowano różnicę na poziomie 7,33 ± 1,58 PU, natomiast w grupie eksperymentalnej o 11,41 ± 2,12 PU (p<0,0005) w porównaniu do wartości przed rozpoczęciem badania. W pozostałych parametrach docelowych nie odnotowano statystycznie istotnych różnic między grupami [35].

W podobnym badaniu Washif i wsp. ocenili skuteczność postępowania usprawniającego w uzupełnieniu z drganiami stochastycznymi w leczeniu lumbago u mężczyzny (powyżej 30 r.ż.) realizującego trening siłowy 3x w tygodniu przez 45–90 min. Dokonano oceny niepełnosprawności spowodowanej dolegliwościami bólowymi kręgosłupa piersiowo-lędźwiowego za pomocą kwestionariusza Oswestry oraz natężenia bólu za pomocą skali numerycznej NRS. Pierwszy etap postępowania fizjoterapeutycznego zawierał stochastyczną wibrację całego ciała (4–5 serii po 90 s, oddzielone przerwami o czasie 30 s, pozycja leżąca), ćwiczenia relaksacyjne, stabilizacji, rozciągające mięśni grzbietu oraz terapię ciepłem w ciągu 3 tygodni. Drugi etap zawierał ćwiczenia zwiększające siłę mięśni grzbietu w ciągu 16 tygodni. Na podstawie kwestionariusza Oswestry odnotowano zmniejszenie bólu i stopnia niepełnosprawności po zastosowaniu 4 i 7 dni zabiegowych odpowiednio o 51% i 8% osiągając poprawę sprawności ruchowej i jakości życia o około 60%. Podobny trend zmian zaobserwowano na podstawie skali NRS z 6 pkt (przed zastosowaniem terapii) do 0–1 pkt po zastosowaniu 11 dni zabiegowych w ciągu pierwszego etapu usprawniania. W drugim etapie usprawniania pacjent nie zgłaszał żadnych skarg dotyczących bólu lub dyskomfortu podczas wykonania ćwiczeń. Autorzy sugerują, że postępowanie fizjoterapeutyczne zastosowane w badaniu własnym ma klinicznie znaczący wpływ na intensywność bólu i zmniejszenie niepełnosprawności, przywracając jednocześnie funkcjonalną mobilność [36].

Blasimann i wsp. przeprowadzili analizę aktywności mięśni prostownika grzbietu i czworobocznego grzbietu (włókna górne i dolne). U 19 kobiet zastosowano częstotliwość 2, 4, 6, 8, 10, 12 Hz bez/z dodatkiem szumu w przedziale 0–5 (zakres zmienności bodźców) w 12 seriach po 10 sekund. Zaobserwowano wzrost wartości maksymalnego skurczu dowolnego (MVC) mięśni prostownika grzbietu o 14,5%, mięśni czworobocznego włókien górnych i dolnych odpowiednio o 7,4% (10 Hz bez szumu) i 4,6% (12 Hz z szumem). Ponadto, różnice aktywności mięśni były istotne w zakresie częstotliwości 6–12 Hz (p≤0,047) w porównaniu do wartości spoczynkowych. Nie odnotowano znaczących różnic w częstotliwości z/bez szumu. Autorzy podkreślają, że aktywność mięśni podczas drgań stochastycznych jest dość niska i porównywalna do ćwiczeń wytrzymałościowych, sensomotorycznych, izolowanych skurczów mięśnia poprzecznego brzucha i stanowi kolejny środek terapeutyczny w profilaktyce zaburzeń mięśniowo-szkieletowych [37]

Lauper M i wsp. porównali wpływ drgań stochastycznych i sinusoidalnie naprzemiennych na aktywność mięśni dna miednicy za pomocą EMG w spoczynku i maksymalnym skurczu dowolnym (MVC). Zaobserwowano znacznie zwiększoną aktywność mięśni dna miednicy wraz ze zwiększonym MVC u kobiet po porodzie stosując drgania stochastyczne o częstotliwości 6-12 Hz w porównaniu do drgań sinusoidalnie naprzemiennych (5–26 Hz, 2–4 mm) odnotowując nieznaczne zmiany aktywności mięśni w stosunku wartości początkowych. Autorzy podkreślają, że ze względu na brak inwazyjności wibracja całego ciała może stanowić kolejny środek terapeutyczny u kobiet, które nie preferują zastosowania elektrostymulacji dopochwowej [38].

Dittrich i wsp. zastosowali drgania stochastyczne (4 ćwiczenia podczas 3 serii po 45–60 s, oddzielonymi przerwami o czasie 30 s, 3x/tydzień w ciągu 12 tyg.) u osób powyżej 60. r.ż. Dokonano oceny w zakresie zawartości tkanki kostnej (BMC), gęstości mineralnej kośćca (BMD), siły skurczów izometrycznych mięśni tułowia, równowagi statycznej i dynamicznej oraz subiektywnego stanu zdrowia. W grupie eksperymentalnej u mężczyzn zaobserwowano wzrost siły mięśni odpowiedzialnych (wykonujących dyspozycje ruchowe) za ruch zgięcia (wartość średnia: o

90,04 N, p=0,002) i w ruchu wyprostu (wartość średnia: o 82,1 N, p=0,002), natomiast u kobiet odnotowano wzrost siły w ruchu zgięcia (wartość średnia: o 34,5 N, p<0,001) i w ruchu wyprostu (wartość średnia: o 55,9 N, p<0,001) w porównaniu do grupy kontrolnej. Co więcej, w grupie eksperymentalnej u kobiet na podstawie testu Wstań i Idź zaobserwowano poprawę o 0,4 s (p<0,001) w porównaniu do stanu przed rozpoczęciem terapii, jak również uzyskany rezultat był lepszy o 0,9 s. (p=0,003) w porównaniu do grupy kontrolnej [39].

ZMIANY HORMONALNE

Zmiany w metabolizmie tryptofanu wzdłuż szlaku kynureninowego zaobserowano w ośrodkowym i obwodowym układzie nerwowym u pacjentów z chorobami neurozapalnymi, neurodegeneracyjnymi oraz w procesie starzenia organizmu. Kepplinger i wsp. zastosowali drgania stochastyczne (10 Hz, 5 serii po 120 s, oddzielone przerwami o 30 s) u 10 zdrowych osób w wieku średnio 33,2±4,1 roku. Dokonano oceny stężeń w surowicy krwi L-tryptofanu, L-kinureniny, kwasu kynureninowego i kwasu antranilowego 1 min przed aplikacją wibracji oraz w 1, 5, 15, 30 i 60 min po zastosowaniu drgań stochastycznych. Zaobserwowano umiarkowane, ale znaczące obniżenie poziomów L-tryptofanu, L-kinureniny i kwasu kinureninowego w surowicy do 60 minut. Poziomy kwasu antraniliowego charakteryzowały się umiarkowanym, nieistotnym statystycznie krótkotrwałym obniżeniem wartości przez okres do 15 min, a następnie normalizacją po 60 min. Współczynniki metabolitów tryptofanu były umiarkowanie zmienne, co sugeruje aktywację metabolizmu po zastosowaniu drgań stochastycznych. Zmiany w metabolizmie L-tryptofanu sugerowałyby większe włączenie aminokwasów w trwającą syntezę białek i tworzenie kości, ponieważ dostępność L-tryptofanu podczas wzrostu kości jest niezbędna. Obniżenie poziomu kwasu kynureninowego w następstwie drgań stochastycznych może być istotne dla redukcji objawów u pacjentów z zaburzeniami neuropsychiatrycznymi, takimi jak choroba Parkinsona, choroba Alzheimera, schizofrenia i depresja [40].

PODSUMOWANIE

Pierwsze doniesienia wstępne dotyczące treningu rezonansem stochastycznym pochodzą z dyscyplin sportowych, w których istnieją duże wymagania w odniesieniu do zachowania balansu ciała i sterowania refleksami. Sportowcy, tacy jak Kati Wilhelm (biathlonistka, siedmiokrotna medalistka olimpijska, medalistka mistrzostw świata, zdobywczyni Pucharu Świata), Hermann Maier (narciarz alpejski, czterokrotny medalista olimpijski, sześciokrotny medalista mistrzostw świata, czterokrotny zdobywca Pucharu Świata), Ronny Eckermann (narciarz uprawiający kombinację norweską, trzykrotny medalista olimpijski, dziesięciokrotny medalista mistrzostw świata, trzykrotny zdobywca Pucharu Świata) oraz piłkarska drużyna narodowa Brazylii stosowali stochastyczną wibracje całego ciała w treningu koordynacji ruchowej [17]. Istotnym wyzwaniem jest z jednej strony to, żeby określone, dostosowane do warunków zewnętrznych odruchy, przebiegały płynnie i pewnie, z drugiej strony procesy te muszą odbywać się w wyjątkowo krótkich ramach czasowych około 100 do 200 milisekund. Zwykle funkcjonuje to na bazie wartości doświadczenia, które wskutek urazu lub schorzenia zostały zaburzone [15]. Inaczej mówiąc, nie jest leczony specyficzny objaw, lecz procesy aktywacji i optymalizacji mechanizmów sterowania ruchem. Zasada treningu rezonansem stochastycznym stanowi przeciwieństwo dla tradycyjnego rozumienia mechanizmów sterowania ruchem. Z reguły próbuje się nie dopuszczać żadnych zakłóceń i w miarę możliwości ograniczać nieprzewidywalne wpływy. Ponad 250 placówek rehabilitacyjnych w Europie korzysta ze stochastycznej wibracji całego ciała. Zarówno w treningu sportowym, jak i w terapii efektywne postępowanie fizjoterapeutyczne charakteryzuje się zasadniczo zróżnicowanymi, dostosowanymi do siebie nawzajem zabiegami [17].

Na podstawie analizy piśmiennictwa oceniającego efektywność stosowania stochastycznej wibracji całego ciała w fizjoterapii sformułowano następujące wnioski:

1. Metoda rezonansu stochastycznego może powodować zmniejszenie lub usunięcie dysfunkcji w wielu jednostkach chorobowych.
2. Ze względu na znaczną heterogeniczność dotyczącą zarówno osób badanych, projektu, metodologii badań oraz braku wyjaśnień niektórych mechanizmów czynnościowych trudno jest sformułować ogólny pozytywny lub negatywny wniosek końcowy.
3. Wymagane są dalsze badania oceniające efektywność stochastycznej wibracji całego ciała w wielu jednostkach chorobowych, w działaniu profilaktycznym oraz treningu sportowym z uwzględnieniem większej liczby uczestników, obiektywnych metod pomiarowych, oddziaływania terapeutycznego w dłuższym okresie czasu oraz systematycznych przeglądów literatury.

PIŚMIENNICTWO

1. Faisal AA, Selen LP, Wolpert DM. Noise in the nervous system. Nat Rev Neurosci. 2008;9(4):292-303.
2. McDonnell MD, Abbott D. What is stochastic resonance? Definitions, misconceptions, debates, and its relevance to biology. PLoS Comput Biol. 2009;5(5):e1000348. doi: 10.1371/journal.pcbi.1000348.
3. Sun Q, Liu H, Huang N et al. Nonlinear restoration of pulse and high noisy images via stochastic resonance. Sci Rep. 2015;5:16183. doi:10.1038/srep16183.
4. Paulsson J. Summing up the noise in gene networks. Nature. 2004;427:415–418.
5. Wang SQ, Song LS, Lakatta EG et al. Ca2+ signalling between single L-type Ca2+ channels and ryanodine receptors in heart cells. Nature. 2001;410:592-596.
6. Shannon CE. A mathematical theory of communication. Bell Syst Tech J. 1948;27:379-423, 623-656.
7. von Neumann J. Probabilistic logics and the synthesis of reliable organisms from unreliable components. Automata Studies. 1956;34:43-99.

8. Collins JJ, Imhoff TT, Grigg P. Noise-enhanced tactile sensation. Nature. 1996;383:769–770.
9. Collins JJ, Priplata AA, Gravelle DC et al. Noise-enhanced human sensorimotor function. IEEE Eng Med Biol Mag. 2003; 22(2):76-83
10. Priplata AA, Niemi JB, Harry JD et al. Vibrating insoles and balance control in elderly people. Lancet. 2003;362(9390):1123-1124.
11. Priplata A, Niemi J, Salen M et al. Noise-enhanced human balance control. Phys Rev Lett. 2002;89(23):238101.
12. Stocks NG, Allingham D, Morse RP. The application of suprathreshold stochastic resonance to cochlear implant coding. Fluct Noise Lett. 2002;2:169–181
13. Morse RP, Morse PF, Nunn TB et al. The effect of Gaussian noise on the threshold, dynamic range, and loudness of analogue cochlear implant stimuli. J Assoc Res Otolaryngol. 2007;8:42-53.
14. Brewster JF, Graham MR, Mutch WAC. Convexity, Jensen's inequality and benefits of noisy mechanical ventilation. J Royal Society Interface. 2005;2:393-396.
15. Rutkowski S, Szczegielniak J. Rezonans stochastyczny w fizjoterapii. Prakt Fizjoter Rehabil. 2013;42:26-29.
16. Lamprecht S, Lamprecht H. Neuroreha bei Multipler Sklerose: Therapie - Sport - Selbsthilf. Georg Thieme Verlag. Stuttgart 2008.
17. Haas CT, Turbanski S, Schmidtbleicher D. Wie gezielte Unordnung im Training für Ordnung in der Bewegung sorgt: zufällige Schwingungen wirken auf Muskel- und Nervenzellen ein. Forschung Frankfurt. 2006;4:19-25.
18. Haas CT. Vibrationstraining, Biomechanische Stimulation und Stochastische Resonanz Therapie. pt_Zeitschrift für Physiotherapeuten. 2008;60:728-789.
19. Haas CT, Turbanski S, Markitz S et al. Stochastische Resonanzin der Therapie von Bewegungsstörungen. Bewegungstherapie und Gesundheitssport 2006;22:58-61.
20. Haas CT, Buhlmann A, Turbanski S et al. Proprioceptive and sensorimotor performance in Parkinson's disease. Res Sports Med. 2006;14(4):273-287.
21. Schmidtbleicher D, Haas CT, Turbanski S. Vibration Training in Rehabilitation. Proceedings of the 23th ISBS Congress. Beijing. 2005:71-79.
22. Kaut O, Becker B, Schneider Ch et al. Stochastic resonance therapy induces increased movementrelated caudate nucleus activity. J Rehabil Med. 2016;48(9):815–818.
23. Haas CT. Neuronale Korrelate apparativ gestützter Trainingsformen. In: Witte K, Edelmann-Nusser J, Sabo A et al. Sporttechnologie zwischen Theorie und Praxis IV. Aachen: Shaker, 2005, 37-48.
24. Kasturi GC, Adler RA. Osteoporosis: nonpharmacologic management. PM R. 2011;3(6):562-572.
25. Herren K, Schmid S, Rogan S et al. Effects of Stochastic Resonance Whole-Body Vibration in Individuals with Unilateral Brain Lesion: A Single-Blind Randomized Controlled Trial: Whole-Body Vibration and Neuromuscular Function. Rehabil Res Pract. 2018;9319258. doi: 10.1155/2018/9319258
26. Suchanowski A, Bartczyk M. Zmiany wybranych zdolności motorycznych na tle funkcji hemodynamicznych osób po udarze mózgu poddanych zabiegom rezonansu stochastycznego. Prom Zdr Ekol. 2017;2:28-35.
27. Bartczyk M, Suchanowski A, Świderski J et al. Skuteczność rezonansu stochastycznego w usprawnianiu równowagi u osób ze stwardnieniem rozsianym. In: XIV Konferencja Polskiego Towarzystwa Fizjoterapii. Pabianice;2018:37-28.
28. Rogan S, Radlinger L, Hilfiker R et al. Feasibility and effects of applying stochastic resonance whole-body vibration on untrained elderly: a randomized crossover pilot study. BMC Geriatr. 2015;15:25. doi: 10.1186/s12877-015-0021-4.
29. Srokowski G, Radzimińska A, Weber-Rajek M et al. Wpływ rezonansu stochastycznego na równowagę dziecka z Mózgowym Porażeniem Dziecięcym = Influence of stochastic resonance on body balance of children with Cerebral Palsy. J Edu Health Sport. 2015;5(12):521-534.
30. Rogan S, Hilfiker R, Schenk A et al. Effects of whole-body vibration with stochastic resonance on balance in persons with balance disability and falls history - a systematic review. Res Sports Med. 2014;22(3):294-313.
31. Elfering A, Arnold S, Schade V et al. Stochastic Resonance Whole-Body Vibration, Musculoskeletal Symptoms, and Body Balance: A Worksite Training Study. Safety and Health at Work. 2013;4:149-155.
32. Haas CT, Hochsprung A, Turbanski S et al. Zu den Effekten mechanischer Schwingungen in der Rehabilitation von spinalen Läsionen. Neuroplasticity Congress. Zürich. 2004:(digital publication,8 Seiten).
33. Rogan S, de Bruin ED, Radlinger L et al. Effects of whole-body vibration on proxies of muscle strength in old adults: a systematic review and meta-analysis on the role of physical capacity level. Eur Rev Aging Phys Act. 2015;12:12. doi: 10.1186/s11556-015-0158-3.
34. Rogan S, Radlinger L, Baur H et al. Sensory-motor training targeting motor dysfunction and muscle weakness in long-term care elderly combined with motivational strategies: a single blind randomized controlled study. Eur Rev Aging Phys Act. 2016;13:4. doi: 10.1186/s11556-016-0164-0.
35. Elfering A, Zahno J, Taeymans J et al. Acute effects of stochastic resonance whole body vibration. World J Orthop. 2013;4(4):291-298.
36. Washif JA, Teichmann J, Kok LY et al. Using stochastic resonance and strength training as part of a rehabilitation programme for recurrent low back pain treatment: a case study. J Exerc Rehabil. 2019;15(1):139-147.
37. Blasimann A, Fleuti U, Rufener M et al. Electromyographic activity of back muscles during stochastic whole body vibration. J Musculoskelet Neuronal Interact. 2014;14(3):311-317.
38. Lauper M, Kuhn A, Gerber R et al. Pelvic floor stimulation: what are the good vibrations? Neurourol Urodyn. 2009;28(5):405-410.
39. Dittrich M, Eichner G, Schmidtbleicher D et al. Eine Untersuchung zur Wirkung der Stochastischen Resonanztherapie (SRT-Zeptoring) auf die Knochendichte, Rumpfkraft und Koordination bei Senioren. OUP : Zeitschrift für die orthopädische und unfallchirurgische Praxis. 2012;1(2):60-65.
40. Kepplinger B, Baran H, Sedlnitzky-Semler B et al. Stochastic resonance activity influences serum tryptophan metabolism in healthy human subjects. Int J Tryptophan Res. 2011;4:49-60.

Konflikt interesów:
Wszyscy autorzy deklarują brak konfliktu interesów

AUTOR KORESPONDUJĄCY

Mateusz Bartczyk
Klinika Rehabilitacji i Medycyny Fizykalnej UM,
Pl. Hallera 1, 90-647 Łódź,
tel./fax: 42 6393064
e-mail: mateusz.bartczyk@o2.pl

Nadesłano: 29.03.2019
Zaakceptowano: 04.06.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

LEGAL BASIS OF PROFESSIONALS' COMPETENCE FORMATION OF EMERGENCY AND MEDICAL SPECIALISTS IN THE FIRST AID APPROACHES

Anatolii M. Hrynzovskyi[1], Serhii V. Bielai [2], Oleksandr V. Tkachenko[2], Serhiy M. Reshetnyk[1], Svitlana I. Kalashchenko[1], Olha S. Koliusheva[2]

[1]EMERGENCY MEDICINE AND TACTICAL MEDICINE DEPARTMENT BOGOMOLETS NATIONAL MEDICAL UNIVERSYTY, KYIV, UKRAINE
[2]NATIONAL ACADEMY OF NATIONAL GUARD OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Introduction: The purpose of educational process in higher educational establishments is to train specialist who has fully mastered the professional competencies for performing daily activities and for action in non-standard situations, which can occur during fulfilling obligations.

The aim: Compare the formation of professional competence and practical skills as important part of increasing effectiveness of specialists training; check the correspondence with current legal acts, which regulate the first aid training.

Materials and methods: The bibliography method, info-analytic method, the comparative method, and logical method were used in our research.

Conclusion: Improvement of complex first aid curriculum for professionals of emergency service is determined the increasing of the level of psychological readiness for performing professional duties.

KEY WORDS: studying methods, first aid, case method, psychological readiness competence, legal documents

Wiad Lek 2019, 72, 7, 1371-1379

INTRODUCTION

Nowadays, it is a great value to apply the acquired knowledge, even in peace or war time. The purpose of educational process in higher educational establishments is to train specialist who has fully mastered the professional competencies for performing daily activities and for action in non-standard situations, which can occur during fulfilling obligations. The purpose of the educational process of the higher educational institutions is to train a specialist who has fully mastered the professional competencies necessary for him both for daily activities and for action in non-standard situations that may arise during the performance of his duties. The specialists of emergency approach (militaries, lifeguards, firefighters, policemen, and paramedics) have to acquire the knowledge of first aid, because they work with hazard to life, injuries, and wounds. There is a necessity to apply first aid for injured people [1]. Paramedics, unlike others specialists, have to know the peculiarities of first aid application in different systems of reaction and combat tasks performance according to current standards (curriculum): PHTLS, TCCC-MP, TCCC-AC, TECC, LEFR-TCC, etc. [2].

The combination of general professional and special competencies forms an integral competence, aimed at further specialist development by improving his qualification level in the system of continuous education. In the first aid field it is becoming up-to-date, because the response protocols and supplying are continually changing.

The current approaches do not consider the peculiarities of personnel actions in every of these systems. We noticed, that current response protocols [3] are combined or even substituted by the lifeguard courses, it is inadmissible for militaries, policemen, firefighters, lifeguards, and for others emergency reaction specialists. There are some differences in first aid application in peace and war time, it is depend on the situation, which happened. For instance, the execution of the cardiopulmonary resuscitation (CPR) in the red zone is dangerous and inefficient, meanwhile, in peace time it is obligatory [4].

Based on the current researches, the statistically significant increase in survival rates among emergency medical care patients is achieved if patients get the first aid no later than 4 minutes after emergency situation occurred [5]. Such early access is possible if witnesses of the event give effective first aid and take measures of basic life support. However, these people cannot substitute medical professionals, but the can help to support life before paramedics come.

THE AIM

The analyzes of educational discipline curriculum "Psychology of emergency activity (including tactical medicine)", higher educational standards, and curriculum in chapter "Military-oriented modules" for training reserve

officers of medical service, particularly module "First aid in emergency situation" which were designed by Military-medical Academy of Ukraine. Compare the formation of professional competence and practical skills as important part of increasing effectiveness of specialists training; check the correspondence with current legal acts, which regulate the first aid training.

MATERIALS AND METHODS

The object of our research is analyzes of some Ukrainian legal documents, which regulate the training of first aid specialists and designing of curriculum of educational discipline "Psychology of emergency activity (including tactical medicine)", which is used for training policemen, law enforcement officials, firefighters; and curriculum in chapter "Military-oriented modules" for training reserve officers of medical service. The comparison of these programs with similar foreign trainings, such as: PHTLS, TCCC-MP, TCCC-AC, TECC, LEFR-TCC, and detection of its advantages and disadvantages.

The bibliography method, info-analytic method, the comparative method, and logical method were used in our research.

REVIEW AND DISCUSSION

First aid is the notion which was updated by the decree of Cabinet of Ministers No. 1115 from 21th of November 2012, which stipulates the application of first aid by the person, who was first near injured, and who does not have medical degree, but has necessary training [6]. Other words, it is self-care and mutual aid with using modern technics and algorithms, aimed at surviving life of injured person. This term is not perfect. Despite of the absence of medical decree of person who gives first aid, his or her actions are aimed at treatment the injured person, and cannot contradict the medical care.

Verkhovna Rada (Parliament of Ukraine) adopted some decrees and orders, which guaranty the right for life and getting medical care for every Ukrainian citizen. Firstly, the Article No. 27 of Ukrainian Constitution declares an indefeasible right to life for every person and citizen of Ukraine. The Article No. 49 of Ukrainian Constitution guaranties the rights for health and medical care. The Decree of Verkhovna Rada (Parliament of Ukraine) about the Recommendation of parliamentary hearing "About Military-medical Doctrine of Ukraine" from 25th of November 2015 [7], the Order No. 275/600 of Ministry of Interior of Ukraine and Ministry of Health of Ukraine from 03rd of April 2018 "About the adoption of Instruction for organizing interoperability with The State Emergency Service and the Ministry of health of Ukraine in case of emergency situations" [8].

During first years of Ukrainian independence the Law of Ukraine No. 2801-XII "Legislation basis of Ukraine about the health care" from 19th of November 1992 which consolidated legal, organizational, economics and social basis of health care of Ukraine; and provisions of medical care for citizens, protection of their health, activity of medical professionals in medical institutions and out of them, moreover, it was given the definition of term "first aid". During next few years our legislation was improved, new decrees and orders which aimed to ensure necessary health and medical care for citizens were adopted, such as: the Order of Ministry of Interior of Ukraine No. 754 from 6th of September 2017 "About the adoption of Instruction of course of action in case of revealing radioactive, chemical and nuclear materials or getting information about the rules violation or illegal usage" which is aimed to provide first aid in case of emergency for those people, who suffered from influence of dangerous materials [9]. The Order of Ministry of Interior No. 50 from 26th of January 2016 "About the adoption of Regulation for organizing employee service training in National Police of Ukraine", which is based on police training methods of providing first aid in case of emergency [10].

The training of personnel, who does not have professional medical decree is regulated by the Law "About emergence first aid"; the Order of Ministry of Health of Ukraine from 29th of March 2017 No. 346 "About the training improvement of providing first aid for those, who do not have professional medical education"; the Order of Ministry of Health of Ukraine from 23rd of August 2018 "About the test formation and administration of people, who obliged to provide hospital and first aid"; the Order of Ministry of Health of Ukraine from 16th of April 2014 No. 398 "About the adoption the orders of providing first aid for people in exigent conditions", which was registered in the Ministry of Justice 7th of July 2014 No. 750/25527; the Order of Ministry of Health of Ukraine from 15th of January 2014 "About adoption and implementation of medical and technical standardization documents of emergency medical aid"; the Regulation of Ministry of Health of Ukraine adopted by the Cabinet of Ministers of Ukraine from 25th of March 2015 No. 267; the Order of Ministry of Health of Ukraine from 2nd of March 2009 No. 132 "About training of non-professional non-medical personnel for application first aid", which was registered in the Ministry of Justice 21st of May 2009 No. 445/16461, for improvement training of non-professional non-medical personnel, who must apply first aid according to their area of responsibility; and for training programs adaptation to international standards of providing emergency first aid.

According to the Regulation of the Cabinet of Ministers of Ukraine from 21st of November 2012 No. 1115 art. 9 and the Order of Ministry of Health of Ukraine from 2nd of March 2009 No. 132 "About training of non-professional non-medical personnel for application first aid" [11], it was suggested to review the list of personnel, who must apply first aid according to their area of responsibility on the scene. The military training program was developed according to the Order of the Ministry of Health of Ukraine No. 322/631/709 from 29th of June 2016 "About the adoption of the Regulations of organization citizen training according to the training program for reserve officers of

medical service". This program was aimed to organize applying of medical and first aid [12].

The activity with high constant risk is always tied with high level of emotional and stressful overpressure. It can become a hard test for young professionals. The person who achieved necessary professional competences during training, could not make decisions and act in extreme conditions [13]. That is why, it is important to conduct workshops during the training process and evaluate not only objective indicators, but also subjective, such as motivation, psychological readiness, and individual qualities, which are characterized particular person [14].

The first aid is studied by emergency reaction professionals, militaries and medics specialists according to the analyses of international experience. It was revealed, that PHTLS (Prehospital Trauma Life Support) [15] is obligatory for all professionals. The Tactical Emergency Casualty Care course (TECC) [16] is outlined as recommendations. It is the basis for rescue civil service. Meanwhile, the Tactical Combat Casualty Care (TCCC) [17, 18] is used for training professionals in case of military conflict.

The PHTLS, TCCC, TECC courses are studied on the basis of international organizations. Its certificates are valid in the USA, European Union and Ukraine: American College of Surgeons (ACS), National Registry of Emergency Medical Technicians (NREMT), American Heart Association (AHA), National Association of Emergency Medical Technicians (NAEMT), National Resuscitation Council (ERC), International Trauma Life Support (ITLS), Army Battlefield Interface Concept (ABIC) [19, 20, 21, 22, 23, 24, 25, 26].

These organizations are non-profit entities; and they trained emergence reaction personnel for application medical aid in case of urgent situation. Depending on the training approach of the courses not only professionals with basic medical decree (paramedics, medical technicians, first aid instructors), but also professionals who must apply first aid according to their area of responsibility on the scene (firefighters, lifeguards, militaries, policemen and special forces) can learn these courses [27].

The first aiders and paramedics learned the course of Tactical Emergency Casualty Care (TECC) [28]. The aim of this course is to teach professionals with basic medical decree how behave in emergence situations in peacetime, and teach new current techniques and algorithms of first aid application. According to this program main tasks are lifesaving, avoidance of additional casualties and continue the execution of combat tasks. The length of this course is 16 hours; it is aimed at reducing mortality rate in case of emergency. The training process consists of lections, practical classes on special training stations, evaluation and tactics tasks. The practical skills include: bleeding control, surgical control of breathing passages, narrow lungs decompression, the algorithm of first aid application on the scene; medical pediatric treatment, and the medical evacuation methods [29]. The evaluation test is after finishing this course, which consists of theoretical part and demonstration of practical skills.

Medic professional achieves such competence as:
- the course of action of first aid application in the direct threat area;
- the methods of first aid application in the indirect threat area;
- the first aid application technics during medical evacuation or in evacuation zone.

The length of the PHTLS [30] course is 16 hours, which includes lections and obligatory practical training on the waxworks under instructors' guidance. The purpose of the Course is teaching paramedics, nurses and doctors of the first aid course of action application. The practical part includes such skills as: primary and secondary patient examining; patient examining according CABCDE, MARCH, AMPLE [31] algorithms; application of tourniquet; Israel bandage; tight dressing; rules of using field dressing Combat Gauze; immobilization of hack-barrows and improvised means; immobilization with SAM and Kendrick splints; immobilization with cervical collar; lungs decompression; occlusal plaster; application of inferior laryngotomy; cardiac compressions; oropharyngeal and nasopharyngeal airways; using pulsimeter; provision of intravenous and inner-boned access; using of mobile ultrasonography; defining of hypothermia and shock indicators. The evaluation tests (introductory and final) are conducted after finishing the course. They consist of tactical task with practical skills demonstration on the waxworks.

As result, professional must get such competences as:
- correct determination of trauma mechanism;
- methods of action coordination on the scene;
- technics of bleeding control;
- bleeding control during medical evacuation in a hospital;
- methods of ensuring clear breathing passages;
- methods of casualty evacuation;
- understanding of the trauma kinematics and recognition of life-threatening injuries;
- technics of injured immobilization;
- prioritization in extreme situation.

The LEFR-TCC [32] course was used for personnel training without special medical decree. If these public order forces know the first aid basis, they will help to save life of injured. This course was designed for personnel without basic medical decree. This course is oriented on training rapid reaction teams and emergency services of basic medical measures, which can help to save life of injured, before professional medical treatment. This course includes PHTLS and TCCC recommendations; and its lengthis 8 hours (lections and practice) [33]. After mastering this course, person will get such skills as; application of tourniquet on arm or leg; using of field dressing; digital vessel occlusion; using of field dressing Combat Gauze; setting of oropharyngeal and nasopharyngeal airways; lungs decompression; occlusal plaster; transport immobilization; defining of shock indicators. The introductory tests are conducted before starting this course; and final tests are conducted after finishing the course.

It is necessary to solve tactical scenario and demonstrate practical skills. After finishing the course, the trained personnel achieve such competences as:

- identification and ways of bleeding control (application of tight bandage, field dressing, tourniquet);
- bleeding control during casualty evacuation to the hospital;
- methods of airways patency by means of some equipment (oropharyngeal and nasopharyngeal airways; lungs decompression; Ambu-bag);
- abilities of shock symptoms indication of casualty.

The Tactical Combat Casualty Care – All Combatants (TCCC-AC) [34] course is aimed to train non-medical personnel and accidental participants of combat situation, hired lifeguards, who occur on the high-risk situation, soldiers and navies. The course length is one day (8 hours); and it consists of lections, practice (using of practical stations under instructors' guidance), tactical scenarios and evaluation control. During this course the professionals will master such skills as: moving of under-jaw; setting of oropharyngeal and nasopharyngeal airways; casualty evacuation in safety place (casualty transportation with strap, dragging by one person, dragging by two people, carrying by two people, carrying on the back); bleeding control with chemicals use (Celox Gauze, ChitoGauze, Combat Gauze), tourniquet, Israel bandage, finding of pulse on radial artery [35].

The TCCC-AC course evaluation control is tests and solving of tactical scenario. After course finishing, the competences which personnel achieve:

- technics of bleeding control;
- technics of airways patency control; method of pin decompression;
- shock symptoms indication;
- using of oral and intramuscular medicine;
- hypothermia prevention;
- first aid course of action in eye penetration trauma, fractures and burns;
- observation of basic vital functions indicators (cardiac activity and respiration).

The Tactical Combat Casualty Care for Medical Personnel (TCCC-MP) [36, 37] course is learned by personnel with basic medical decree (doctors, nurses and paramedics), who may occur on the battlefield or in battle zone. The length of the course is 2 days (16 hours) with lections, practice on the special stations on waxworks. There are main practical skills, which professional have to master: tourniquet application; external bleeding control; field dressing application; wound tamponade; bleeding control with chemical use (haemostatic gauze bandage, applicator); setting of oropharyngeal and nasopharyngeal airways; inferior laryngotomy providence; lungs decompression; provision of intravenous and inner-boned access; methods of infusion using with tranexone and intravenous ketamine infusion; casualty evacuation in safety place (casualty transportation with strap, dragging by one person, dragging by two people, carrying by two people, carrying on the back) [38]. The evaluation control consists of two stages (introductory and final) and solving practical scenario.

Medic professional will achieve such competences as:

- technics of bleeding control (application of tourniquet), activity in CUF zone;
- technics of airways patency control (inferior laryngotomy), breath control (pin decopmression), activity in TFC zone;
- provision of intravenous access, infusion therapy, shock diagnosis and treatment; fractures and burns treatment; analgesia principles in battle zone;
- cerebral injury diagnostics, hypothermia prevention;
- mastering of 9-lines information transmitting system in casualty evacuation (TACEVAC); medical sorting;
- rules of enemy treatment.

The modern international first aid protocols, such as TCCC, Basic Life Support (BLS) [39]; western experience of Denver Department of Health of First Aid concerning are the basis of medical professionals training. The TECC, TCCC, PHTLS [40, 41] recommendations are basic for curriculum chapter "Military orientation modules" for training reserve officers of medical service. The modules "The basic organization of medical provision of civil population and militaries" and "The first aid in extreme situations" include the peculiarities of training professionals of such spheres as: medicine, dentistry, medical psychology, pharmacy.

The basis of the program is measures and urgent actions aimed at saving and preserving the lives of the victim, carried out at the scene by persons with basic medical education. The curriculum of training discipline "Psychology of emergency activity (including tactical medicine)" for cadets of the National Academy of National Guard of Ukraine (NANGU) has a special approach which is based on psychology training of militaries and their adaptation to extreme life conditions. The first aid course is studied less, than the basics of psychology and psychological support of the soldier, however, it does not meet the requirements of LEFR-TCC – program of special forces training [42], which is closed to standard TCCC-AC program.

The are some objective characteristics of curriculums for their comparison:

1. Length of training;
2. Purpose of training;
3. Scope of practical skills;
4. Main competences;
5. Evaluation form (including the acquisition of practical skills).

The length of the course for medical students is 90 hours, including practice – 50 hours; and self-studying – 40 hours. In the National Academy of National Guard of Ukraine, the length of the course is 90 hours, practice training – 32 hours; collective training – 12 hours; lections – 10 hours; self-studying – 36 hours. The ratio of the number of hours for classes and individual work is 54/36 hours. The purpose of the most practical classes and workshops is aimed at better learning of practical skills in application first aid and its course of action.

Through the medics training, the practical classes are conducted in training form. The training form is more useful in acquiring practical skills, than workshops; because training form is focused on working out basic manipulations that will be necessary both in professional activity and in everyday

life. The main purpose of the medical students studying is to achieve competences according to Standard of doctors training and first aid application in emergency situations in peacetime and combat environment. Firstly, it includes some common competences such as: ability to use knowledge in practical situation; ability to choice communication strategy; ability to team-working; ability to interpersonal cooperation; the ability to abstract thinking, analysis and synthesis; and the ability to learn. Secondly, there are some special (professional) competences of medics' students such as: ability to perform evacuation; ability to define tactics of application emergency medical treatment; skills of application emergency medical treatment; skills of performing medical manipulations.

The purpose of NANGU cadets studying includes organization and first aid application to militaries; theoretical and practical training of servicemen in the field of extreme and crisis psychology.

The cadets of NANGU have to master such competences as: the methods of first aid application during execution of combat tasks; the ways of casualty evacuation; knowing main types of extreme situations; knowing human mental condition, behavior and actions in extreme situations; knowing main crowds types; social-psychological principles and mechanisms of human determination; ability of timely first aid application with injuries, poisoning, pneumocardial disorder; individual or team casualty evacuation; providence of emergency psychological support for militaries, who were effected of strong psycho-traumatic shock during execution of combat tasks; be able to give first aid on the battle field and in shelter area; master the methods of extreme psychological and negative emotions regulation; stress-relief methods; visual psychognosis of people during combat operations.

Both curriculums include requirement of mastering basic courses of first aid application and medical professional training peculiarities.

The future medical professionals have to have certain scope of practical skills in first aid application:

- the peculiarities of the scene evaluation, course of action of first aid application

in the shelling and shelter sectors, primarily examining, examining according to CABCDE algorithm, the definition of the level of consciousness on the APVU scale;

- indications and techniques of temporary bleeding stopping, imposing a pressed bandage (Israeli band), application of tourniquet, indications and rules of chemicals using to stop the bleeding;
- technics of airway patency (throwing the head; moving the lower jaw; inserting the nasopharyngeal and oral air ducts); artificial ventilation techniques (mouth to mouth, mouth to nose, mouth to face mask, AMBU bag), moving the injured person to stable lateral position;
- transport immobilization by means of scheduled and adapted means, technique of applying bandages for wounds of the skull, eye, ears, lower jaw;
- first aid application to burns, frostbite, hypothermia, electric shock (lightning);
- first aid application to numbness, coma of unknown etiology, convulsions, heart pain (angina pectoris, heart attack), stroke, abdominal pain, poisoning with an unknown substance or unknown gas;
- water assistance: recognition of the drowned man, approaching, transport to the shore;
- first aid in potent poisoning substance deprivation; first aid in combat and non-combat conditions with radiative action;
- algorithms of medical sorting; fill the MIST-report; methods of casualty transportation from shelter zone to casualty assembly point (by one person, two people with using improvised means); rules of evacuation request; loading and unloading of casualties in various evacuation vehicles; vital signs control during casualty transportation in combat and non-combat conditions;
- mechanisms of coping with stress for medics professionals; technologies of prevention post-traumatic disorder; main principles of first aid application in battle in combat fatigue and combat stress.

The cadets of NANGU achieve such practical skills as: casualty transportation; self-aid and mutual-aid in red and yellow zones; first aid with convulsion and unconsciousness; bleeding control with tourniquet; wound tamponade; secondary casualty examining; conducting cardiopulmonary resuscitation; application of splints; application of extreme psychological regulation; application of auto training; knowing the pain control methods; knowing methods of fear control; procedure of strong-willed mobilization; provide psychological first aid in raving, delusion, nervous tremor, crying, hyperkinesis, stupor, aggression, hysterics, fear.

Medical students are studying according to ECTS; they have to get minimum act score; the evaluation is based on scoring system (from 120 to 200 grade). The exam is form of training evaluation. It is standardized; and consists of theoretical and practical training evaluation. Special focus is on students` practical skills mastering; there are three running tests, which take place on practical lesson. The number of running tests is three, and maximum score is 6 grades. The cadets of NANGU are evaluated by the national evaluation scale and ECTS (A, B, C, D, E, FX, F). The final evaluation test is exam with mark. There are no additional evaluation tests of practical skills according to the curriculum.

The evaluation training systems have great differences. The practical part is main for medical and non-medical professionals according to PHTLS, TCCC-MP, TCCC-AC, TECC, LEFR-TCC training programs [43].

Comparing PHTLS, TCCC-MP, TCCC-AC, TECC, LEFR-TCC training programs with curriculums "Psychology of emergency activity (including tactical medicine)", "First aid in emergency situation" according to objective indicators (table I), is obvious that the competences formation depends on the legth of the course, personnel, and scope of practical skills. The common and special competences are achieved by training according to PHTLS, TCCC-MP, TECC, "Psychology of emergency activity (including tac-

Table I. The comparison of foreign and domestic first aid curriculums

Title of program	Length of the course (hours)	Personnel	Scope	PS Evaluation	Achieved competences
PHTLS	16	Medical professional	full	+	Common and special
TCCC-MP	16	Medical professional	full	+	Common and special
TCCC-AC	8	Non-medical professional	shorten	+	Common
TECC	16	Medical professional	full	+	Common and special
LEFR-TCC	8	Non-medical professional	shorten	+	Common
PES	90	Non-medical professional	shorten	Not specified	Common and special
FAinES	90	Medical professional	full	+	Common and special

Note: PES - "Psychology of emergency activity (including tactical medicine)", FAinES – "First aid in emergency situation", PS – practical skills.

tical medicine)", "First aid in emergency situation"; which form the integrative competence. Only common competences are achieved according to TCCC-AC i LEFR-TCC programs.

The shooting training is a part of tactical medicine according to the NANGU cadets training plan. The important stage of personnel training is: cadets or students competences mastering; psychological readiness of performing combat tasks; motivation for further development and self-education [44]. All-important competences should be laid down during practical classes and seminars, where the teacher is interested and encouraged the student to study the discipline.

The competence formation process consists of four stages [45], so called "rule of 4 needs": need to know, need to manage, need to will and need to act. For instance, third stage is assumed, that professional will make a decision if he/she will give first aid for injured or will stay away, for avoiding deterioration. According to M.I. Pyrohov: "Any school is glorified not by the number, but by the honor of its students" – this rule is regards to psychological readiness of professional to perform combat tasks, which includes such factors as:

1. Motivational – motives, which stipulate occupational choice;
2. Cognitive – theoretical knowledge;
3. Operational – availability of necessary professional skills;
4. Personal – complex of individual and psychological qualities.

Motivational and personal factors have to be developed at the beginning of students studying or during training process; cognitive and operational factors have to be developed through educational process [46].

Thus, summing-up, the educational process have to consists of some stages for better professional formation and mastering practical skills, which are the priority of first aid training [47]:

- 1st stage – theoretical training;
- 2nd stage – teacher`s skill demonstration;
- 3rd stage – student considers courses of action and perform them on waxworks; and after mistakes discussion;
- 4th stage – students hone skills without prompts and comments, which helps enhance the capabilities.

Furthermore, it is possible to define 5th stage, when first aid training takes place in real time; but it would be difficult without additional inventory and logistics management (mannequin, moulage, tourniquet, cervical collar, etc.).

The stage-by-stage approach of studying is modern teaching and educational complex, which will improve of mastering practical skills and motivate for further self-education through advanced training. A case study is a good instrument of mastering first aid courses of action on the lessons (case study is non-game simulated method of situational analysis, based on the studying of solving particular tasks (cases) and real events) [48].

As an example of this method is problem solving, when person was hit by car and she/he is unconscious. There are only improvised means in rucksack and pockets. Under these conditions, it is necessary to give proper first aid for saving casualty and gain time, until ambulance arrives.

The training process on case method base consists of some stages. The individual training is on the first stage; team training (3-4 members) and course of action adjustment is on the second stage; on third stage is group discussion with teachers [49].

Moreover, the timely and consistent casualty transportation from battlefield and others emergency field is an important part of the first aid training process [50]. Thus, special focus must be on the casualty sorting, preparations for transportation, medical treatment during evacuation of NANGU cadets and medical professionals training.

CONCLUSIONS

Nowadays, there is the legal base in Ukraine, which is background for personnel training, who does not have medical decree, but obliged to provide first aid according to the area of responsibility. The special focus must be on the Order of Ministry of Health of Ukraine from 16th of April 2014 No. 398 "About the adoption the orders of providing first aid for people in exigent conditions", which was registered in the Ministry of Justice 7th of July 2014 No. 750/25527, which defines first aid courses of action in different situations; defines the algorithms of first aid application including curriculums and courses, which were mentioned above.

The military and medical training problems remain relevant on all stages of educational process (as well medical and non-medical personnel). It is necessary to focus on using international curriculums of training, which will provide proper level of knowledge and skills in real emergence situations and combat operations. Thus, in accordance with the requirements of the curriculum, the use of different teaching methods will contribute to a better understanding of the practical skills of the first aid which includes:

Firstly, after analyzing current first aid curriculums of different countries and comparing them with domestic ones, it is necessary to summarize, that length of training program, the training form, involved personnel, the scope of practical skills are influenced on achieving common and special competences. Different approaches of results evaluation and forms of intermediate tests of practical skills influence on competence formation of emergency and medical professionals.

Secondly, the improvement of complex first aid curriculum for professionals of emergency service including some peculiarities is determined the increasing of the level of psychological readiness for performing professional duties. The application of modern training forms and methods with frequent demonstration of practical skills is allowed to transform knowledge into skills of first aid application.

Thirdly, the using of case methods helps to practice courses of action which occur in emergency situation, and teach team-work and cooperation with strangers in extreme conditions. The using of modern educational first aid technologies increases the level of mastering practical skills, which are necessary for saving life of casualty.

Forth, safety issue of applying first aid is one of priorities in first aid training for all professionals. Particularly, it is necessary to mention, that shooting training is important not only for professionals, who plan to become reserve officers.

Suggested approaches are required further research and discussion, they can be the subjects of special study in other our articles.

REFERENCES

1. Jacobs L.M., Burns K.J. Improving Survival From Intentional Mass Casualty Incidents The Need for a National Curriculum. JAMA Surgery. 2014; 149(9): 891-892. doi: 10.1001/jamasurg.2014.189.
2. National Association of Emergency Medical Technician (NAEMT) [Electronic resource]. - Mode access: http://www.naemt.org
3. Mazurenko O.V., Roshchin H.H., Voloshyn V.O. Taktychna medytsyna yak osnovna skladova ekstrenoyi medychnoyi dopomohy pry provedenni antyterorystychnykh operatsiy. [Tactical medicine as a key of emergency medical care during anti-terrorist operations] Medytsyna neotlozhnykh sostoyanyy. 2014; 8 (63):96-99. (in Ukrainian).
4. Tactical Emergency Casualty Care (TECC) Guidelines Current as of June 2015 [Electronic resource]. - Mode access: http://www.c-tecc.org/images/content/TECC_Guidelines_-_JUNE_2015_update.pdf
5. Ovcharuk I.S., Tverezovs'kyy M.V., Minasov R.V. et al. Taktychna medytsyna. Alhorytm domedychnoyi dopomohy pid chas boyovykh diy [Tactical medicine. Algorithm of rendering pre-medical aid in conditions of military operations]. Aktual'ni problemy transportnoyi medytsyny. 2015. 3, 2 (41-II): 50-52. (in Ukrainian).
6. Chuprina O.V., Zhylin T.P. Aktual'ni problemy vykladannya domedychnoyi dopomohy pratsivnykam natsional'noyi politsiyi Ukrayiny [Actual Problems of Providing Medical Assistance to National Police Officers] Naukovyy visnyk Natsional'noyi akademiyi vnutrishnikh sprav. 2017; 4 (105): 175 (in Ukrainian).
7. Kontseptsiya reformy systemy ekstrenoyi medychnoyi dopomohy [Electronic resource]. - Mode access: http://moz.gov.ua/uploads/1/5592-pro_20180615_1_dod.pdf (in Ukrainian).
8. Postanova Verkhovnoyi Rady Ukrayiny pro Rekomendatsiyi parlament•s'kykh slukhan' na temu «Pro viys'kovo-medychnu doktrynu Ukrayiny» vid 25.11.205 roku. [Electronic resource]. - Mode access: http://zakon.rada.gov.ua/laws/show/827-19/sp:max100 (in Ukrainian).
9. Nakaz № 275/600 MVS Ukrayiny ta MOZ Ukrayiny vid 03.04.2018 «Pro zatverdzhennya Instruktsiyi shchodo orhanizatsiyi vzayemodiyi mizh Derzhavnoyu sluzhboyu Ukrayiny z nadzvychaynykh sytuatsiy i Ministerstvom okhorony zdorov'ya Ukrayiny v razi vynyknennya nadzvychaynykh sytuatsiy». [Electronic resource]. - Mode access: http://zakon.rada.gov.ua/laws/show /z0479-18/sp:max100 (in Ukrainian).
10. Nakaz MVS Ukrayiny № 754 vid 06.09.2017 «Pro zatverdzhennya Instruktsiyi pro poryadok diy orhaniv (pidrozdiliv) politsiyi v razi vyyavlennya radioaktyvnykh, khimichnykh ta yadernykh materialiv abo otrymannya informatsiyi pro porushennya pravyl chy nezakonne povodzhennya z nymy». [Electronic resource]. - Mode access: http://zakon.rada.gov.ua/laws/show/z1240-17/sp:max100 (in Ukrainian).
11. Nakaz MVS Ukrayiny №50 vid 26.01.2016 «Pro zatverdzhennya Polozhennya pro orhanizatsiyu sluzhbovoyi pidhotovky pratsivnykiv Natsional'noyi politsiyi Ukrayiny». [Electronic resource]. - Mode access: http://zakon.rada.gov.ua/laws/show/z0260-16/sp:max100 (in Ukrainian).
12. Moroz Ye. D., Blyznyuk M.D., Yelishevs'kyy B.M. et al. Propozytsiyi shchodo perevirky yakosti znan' z nadannya domedychnoyi dopomohy u osib bez medychnoyi osvity [Proposals on the quality control of knowledge on the provision of medical assistance to persons without medical education]. VII Mizhnarodnyy medychnyy konhres «Vprovadzhennya suchasnykh dosyahnen' medychnoyi nauky u praktyku okhorony zdorov"ya Ukrayiny».2018:34-35 (in Ukrainian).
13. Nakaz MOZ Ukrayiny № 322/631/709 vid 29.06.2016 «Pro zatverdzhennya Instruktsiyi pro orhanizatsiyu viys'kovoyi pidhotovky hromadyan Ukrayiny za prohramoyu pidhotovky ofitseriv zapasu medychnoyi sluzhby». [Electronic resource]. - Mode access: http://zakon.rada.gov.ua /laws/show/z1070-16/sp:max100 (in Ukrainian).
14. Butler F.K. Tactical combat casualty care: beginnings . Wilderness Environ Med. 2017; 28: 12–17. doi: 10.1016/j.wem.2016.12.004
15. Scerbo M.H. Mumm J.P., Gates K. et al. Safety and appropriateness of tourniquets in 105 civilians. Journal Prehospital Emergency Care. 2016; 20 (6): 712-722. doi: 10.1080/10903127.2016.1182606
16. Callaway D.W. Translating Tactical Combat Casualty Care Lessons Learned to the High-Threat Civilian Setting: Tactical Emergency Casualty Care and the Hartford Consensus . Wilderness Environ Med. 2017; 28(2S): 140-145. doi: 10.1016/j.wem.2016.11.008
17. Callaway D.W., Smith E.R., Cain J. et al. Tactical emergency casualty care (TECC): guidelines for the provision of prehospital trauma care in high threat environments. J Spec Oper Med. 2011; 11: 104–122.
18. Yakovtsov I.Z., Zahurovs'kyy V.M., Lykhman V.M. et al. Pedadohichni osoblyvosti navchannya nemedychnykh pratsivnykiv ekstrenoyi medychnoyi dopomohy [Pedagogical peculiarities of training non-medical emergency workers]. Zhurnal «Medytsyna neotlozhnykh sostoyanyy». 2013; 2 (49) [Electronic resource]. - Mode access: http://www.mif-ua.com/archive/article_print/35551 (in Ukrainian).

19. American College of Surgeons (ACS) [Electronic resource]. - Mode access: https://www.facs.org
20. American Heart Association (AHA) [Electronic resource]. - Mode access: https://www.heart.org/
21. European Resuscitation Council (ERC) [Electronic resource]. - Mode access: https://www.erc.edu
22. International Trauma Life Support (ITLS) [Electronic resource]. - Mode access: https://www.itrauma.org
23. Army Basic Instructor Course (ABIC) [Electronic resource]. - Mode access: https://www.png.pa.gov/army_national_guard/166th_regiment/2ndbn/Pages/ABIC-Army-Basic-Instructor-Course.aspx
24. Holcomb J., Butler F., Rhee P. Hemorrhage control devices: tourniquets and hemostatic dressings .The Journal of Special Operations Medicine (JSOM). 2015; 15: 153–156.
25. Jacobs L.M., Wade D., McSwain N.E. et al. Hartford Consensus: A Call to Action for THREAT, a Medical Disaster Preparedness Concept. Journal of the American College of Surgeons. 2018; 218 (6): 467–475
26. The National Registry of Emergency Medical Technicians (NREMT) [Electronic resource]. - Mode access: https://www.nremt.org
27. Evdokimov V.I., Chernov K.A. Medytsyna katastrof: ob"yekt vyvchennya i nauko metrychnyy analiz vitchyznyanykh naukovykh statey (2005-2017 roky) [Disaster medicine: an object of study and a scientometric analysis of domestic scientific articles (2005-2007 years)]. Medyko-biolohichni i sotsial'no-psykholohichni problemy bezpeky v nadzvychaynykh sytuatsiyakh. 2018; 3: 98-117 (in Ukrainian).
28. Tactical Emergency Casualty Care (TECC) [Electronic resource]. - Mode access: https://www.naemt.org/education/tecc
29. Shapiro G., Sarani B. Tactical Emergency Casualty Care (TECC): Principles and Practice. Front Line Surgery. In: Matthew J. Martin, Alec C. Beekley, Matthew J. Eckert et al. Front Line Surgery: A Practical Approach . USA: Springer: 2017, p. 711-725. doi: 10.1007/978-3-319-56780-8_41
30. Prehospital Trauma Life Support (PHTLS) [Electronic resource]. - Mode access: https://www.naemt.org/education/phtls
31. Montgomery H.R., Butler F.K., Kerr W. et al. TCCC Guidelines Comprehensive Review and Update. TCCC Guidelines Change 16-03. J Spec Oper Med. 2017; 17(2):21-38.
32. Law Enforcement and First Response Tactical Casualty Care (LEFR-TCC) [Electronic resource]. - Mode access: https://www.naemt.org/docs/default-source/about-us-documents/annual-reports/naemt_2015annualreport.pdf
33. TCCC for All Combatant (TCCC-AC) [Electronic resource]. - Mode access: https://www.naemt.org/education/naemt-tccc/tccc-ac-guidelines-and-curriculum
34. Jacobs L.M., Burns K.J., Pons P.T. et al. Initial Steps in Training the Public about Bleeding Control: Surgeon Participation and Evaluation. Journal of the American College of Surgeons. 2017; 224:1084-1090 doi: 10.1016/j.jamcollsurg.2017.02.013.
35. TCCC for Medical Personnel (TCCC-MP) [Electronic resource]. - Mode access: https://www.naemt.org/education/naemt-tccc/tccc-mp-guidelines-and-curriculum
36. Tactical Combat Casualty Care (TCCC) [Electronic resource]. - Mode access: https://www.naemt.org/education/naemt-tccc
37. Krammel M., Schnaubelt S., Weidenauer D. et al. Gender and age-specific aspects of awareness and knowledge in basic life support. PLoS One. 2018; 13(6):e0198918. doi: 10.1371/journal.pone.0198918.
38. Roshchin G.G., Daniel Smile. Pidhotovka likariv ta viys'kovosluzhbovtsiv sylovykh vidomstv za prohramamy taktychnoyi medytsyny T•SSS ta TESS. [Training of physicians and military personnel of the security agencies under TCCC and TECC tactical medication programs]. Materialy konhresu «Problemni pytannya medytsyny nevidkladnykh staniv: teoretychni ta praktychni aspekty». 2015; 154-155. (in Ukrainian).
39. Young J.B., Sena M.J., Galante J.M. Physician roles in tactical emergency medical support: the first 20 years. J Emerg Med. 2014; 46(1):38-45.
40. Cornelius B., Campbell R., McGauly P. Tourniquets in trauma care: a review of application. Journal of Trauma Nursing. 2017; 24(3): 203-207. doi: 10.1097/JTN.0000000000000290.
41. Jacobs L.M., Burns K.J Tourniquet application training for individuals with and without a medical background in a hospital setting. Journal of the American College of Surgeons. 2015; 78(2): 442–445. doi: 10.1097/TA.0000000000000505.
42. Barco V.I., Ostapovich V.P., Barko V.V. Napryamy vdoskonalennya profesiynoyi psykholohichnoyi pidhotovky politseys'kykh natsional'noyi politsiyi Ukrayiny [The ways of improvement of professional psychological training of ukrainian national police officers]. PSYCHOLOGICAL JOURNAL. 2018; 4 (14): 9-18. doi: 10.31108/2018vol14iss4pp9-18 (in Ukrainian).
43. Navchannya navychkam nadannya pershoyi dolikars'koyi dopomohy [Electronic resource]. - Mode access: http://zw.ciit.zp.ua/index.php/Навчання_навичкам_надання_першої_долікарської_допомоги (in Ukrainian).
44. Baruch E.N., Benov A., Shina A. et al. Does practice make perfect? Prospectively comparing effects of 2 amounts of practice on tourniquet use performance. The American Journal of Emergency Medicine. 2016; 34(12): 2356-2361
45. Baruch E.N., Kragh Jr J.F., Berg A.L. et al. Confidence–competence mismatch and reasons for failure of non-medical tourniquet users. Journal Prehospital Emergency Care. 2017; 21(1): 39-45. doi: 10.1080/10903127.2016.1209261.
46. Gudzevich L.S. Formy ta metody navchannya studentiv domedychnoyi dopomohy [Forms and methods of teaching students of medical assistance]. Suchasni problemy biolohichnoyi nauky ta metody yiyi vykladannya u zakladakh vyshchoyi osvity: zbirnyk naukovykh prats' zvitnoyi naukovoyi konferentsiyi vykladachiv za 2017-2018 n.r. Vinnytsya: TOV «Nilan-LTD». 2018; 318: 135-145 (in Ukrainian).
47. Tarasyuk V.S., Matviichuk M. V., Koroleva N.D. et al. Umovy ta neobkhidnist' vyvchennya dystsypliny «Persha medychna dopomoha v ekstremal'nykh sytuatsiyakh» u medychnykh vyshchykh navchal'nykh zakladakh [Conditions and the necessity of studying the course "first medical aid in extreme situations" in medical universities]. Biomedical and Biologycial Anthropology. 2016; 26: 189-192 (in Ukrainian).
48. Gudzevich L.S. Vykorystannya keys tekhnolohiy pry vykladanni navchal'noyi dystsypliny «Sestryns'ka sprava» [Using case technology when teaching discipline "nursing practice"]. Aktual'ni pytannya heohrafichnykh, biolohichnykh ta khimichnykh nauk. Osnovni naukovi problemy ta perspektyvy doslidzhennya . Zbirnyk naukovykh prats' VDPU. Vinnytsya. 2017; 14 (19): 70-72 (in Ukrainian).
49. David H., Stefan K.B., Marzellus H. et al. Quality of Documentation as a Surrogate Marker for Awareness and Training Effectiveness of PHTLS-Courses. Part of the Prospective Longitudinal Mixed-Methods EPPTC-Trial. PLoS One. 2017; 12(1). doi: 10.1371/journal.pone.0170004
50. Iskra N.I., Blyznyuk M.D., Pechyborshch V.P. et al. Tsyvil'na ta viys'kova systema okhorony zdorov"ya, osoblyvosti vzayemodiyi pid chas boyevykh diy [Civilian military health system, features of interaction during combat operations]. Zb. nauk. prats' spivrobit. NMAPO imeni P.L. Shupyka. 2015; 24 (4): 172-179 (in Ukrainian).

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Anatoliy Hrynzovskyi
Department of Emergency Medicine and Tactical Medicine
Bogomolets National Medical University
T. Schevchenka blvd., 13, Kyiv 01601, Ukraine
tel: +380503876426
e-mail: grin_am@ukr.net

Received: 28.02.2019
Accepted: 03.06.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

PRENATALNA OPERACJA PRZEPUKLINY OPONOWO-RDZENIOWEJ – SZANSA NA POPRAWĘ JAKOŚCI ŻYCIA

PRENATAL MYELOMENINGOCELE REPAIR – A CHANCE TO IMPROVE THE QUALITY OF LIFE

Agnieszka Pastuszka[1], Janusz Bohosiewicz[2], Anita Olejek[3], Jacek Zamłyński[3], Ewa Horzelska[3], Tomasz Koszutski[4]
[1]KATEDRA I ZAKŁAD ANATOMII OPISOWEJ I TOPOGRAFICZNEJ, WYDZIAŁ LEKARSKI Z ODDZIAŁEM LEKARSKO-DENTYSTYCZNYM W ZABRZU, ŚLĄSKI UNIWERSYTET MEDYCZNY W KATOWICACH, KATOWICE, POLSKA
[2]WYŻSZA SZKOŁA PLANOWANIA STRATEGICZNEGO W DĄBROWIE GÓRNICZEJ, DĄBROWA GÓRNICZA, POLSKA
[3]KATEDRA I ODDZIAŁ KLINICZNY GINEKOLOGII, POŁOŻNICTWA I GINEKOLOGII ONKOLOGICZNEJ, WYDZIAŁ LEKARSKI Z ODDZIAŁEM LEKARSKO-DENTYSTYCZNYM W ZABRZU, ŚLĄSKI UNIWERSYTET MEDYCZNY W KATOWICACH, KATOWICE, POLSKA
[4]KLINIKA CHIRURGII I UROLOGII DZIECIĘCEJ, WYDZIAŁ LEKARSKI W KATOWICACH, ŚLĄSKI UNIWERSYTET MEDYCZNY W KATOWICACH, KATOWICE, POLSKA

STRESZCZENIE

Rozszczep kręgosłupa (*spina bifida, myelomeningocele*) jest najczęstszą wadą rozwojową układu nerwowego. Częstość jej występowania wynosi w różnych rejonach świata od 0,3–5 na 1000 żywo urodzonych noworodków. Wada powstaje we wczesnym etapie życia płodowego jednak, jak dotychczas nie wykazano jednoznacznie jej przyczyny. Aktualnie uważa się, że jednym z najistotniejszych czynników prowadzących do wystąpienia *myelomeningocele* jest niedobór kwasu foliowego w organizmie matki przed ciążą i w czasie jej trwania. Pierwsze próby leczenia rozszczepu kręgosłupa były podejmowane już w starożytności. Rozwój wiedzy na temat etiologii i skutków *spina bifida* oraz rozwój technik chirurgicznych pozwoliły na wprowadzenie nowych metod leczenia nie tylko samej wady, ale także powikłań z nią związanych. Od 20 lat w Stanach Zjednoczonych i od 12 lat w Europie (Polska i Szwajcaria) przeprowadzane są prenatalne operacje rozszczepu kręgosłupa. Analiza porównawcza pacjentów operowanych prenatalnie i postnatalnie z powodu *myelomeningocele* wykazała, że dzieci operowane prenatalnie ponad dwukrotnie rzadziej wymagają założenia zastawki komorowo-otrzewnowej z powodu wodogłowia. Prenatalna operacja przepukliny oponowo-rdzeniowej dzięki skróceniu czasu ekspozycji rdzenia kręgowego i nerwów rdzeniowych na toksyczne działanie płynu owodniowego oraz ekspozycji na urazy mechaniczne zwiększa szansę na poprawę funkcji układów ruchu, moczowego i pokarmowego, dzięki czemu w sposób istotny statystycznie poprawia jakość życia dzieci z rozszczepem kręgosłupa.

SŁOWA KLUCZOWE: rozszczep kręgosłupa, operacje prenatalne, jakość życia

ABSTRACT

Spina bifida (*myelomeningocele*) is the most prevalent developmental defect of the nervous system. In different regions of the world it affects from 0.3 to 5 per 1000 of living neonates. It is known that the defect develops during the early fetal life however no explicit cause has been found yet. Recently it has been accepted that one of the major factors contributing to spina bifida is deficiency of folic acid in the mother's body before and during pregnancy. The first attempts to cure myelomeningocele were taken in ancient times. More extensive knowledge of aetiology and effects of spina bifida and development of new surgical techniques allowed for management not only of the defect itself but also the consequent complications. Prenatal spina bifida repair has been performed in the USA for 20 years now while European surgeons (Poland and Switzerland) have operated myelomeningocele for 12 years. Comparative analysis carried out to evaluate the patients operated for spina bifida prenatally and postnatally pointed that those after fetal repair demand the use of ventriculoperitoneal shunt for hydrocephalus twice less frequently. Thanks to shortened exposure of the spinal cord and the spinal nerves to the toxic effect of amniotic fluid and reduced exposure to mechanical injuries, prenatal *myelomeningocele* repair offers better opportunities to improve motor, urinary and alimentary functions, contributing then statistically to higher quality of lives of children with spina bifida.

KEY WORDS: spina bifida, prenatal surgery, quality of life

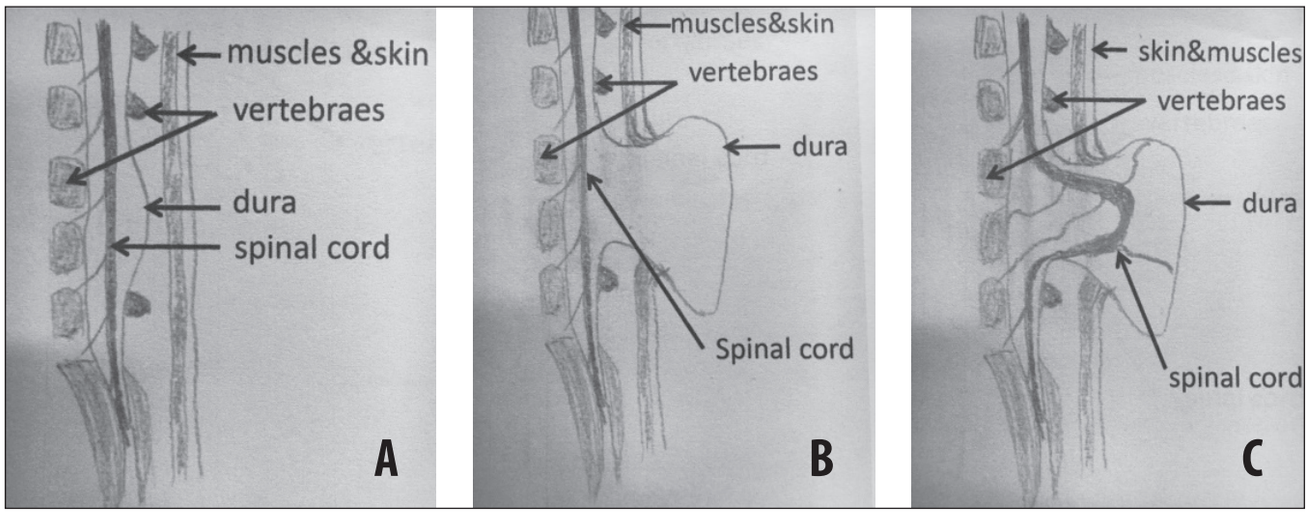
Wiad Lek 2019, 72, 7, 1380-1386

WSTĘP

Przepuklina oponowo-rdzeniowa to najczęstsza wada rozwojowa układu nerwowego i druga co do częstości występowania (po wadach serca) wada wrodzona.

Częstość jej występowania wynosi w różnych rejonach świata od 0,3–5 na 1000 żywo urodzonych noworodków. Takie zróżnicowanie w liczbie urodzeń dzieci z przepukliną oponowo-rdzeniową na świecie jest najpewniej związane z różnym poziomem ekonomicznym, akceptacją terminacji ciąży oraz dostępnością do usług medycznych w różnych krajach [1–3].

Wada ta polega na zaburzeniu neurulacji cewy nerwowej oraz nie spojeniu kręgów i może dotyczyć każdego odcinka



Ryc. 1. Przepuklina oponowo-rdzeniowa- postać tylna wady:
A. przepuklina oponowo-rdzeniowa zamknięta;
B. przepuklina oponowa otwarta;
C. przepuklina oponowo-rdzeniowa otwarta.

kręgosłupa. Najczęściej jest zlokalizowana na poziomie kręgosłupa lędźwiowego (około 62%), rzadziej w odcinku krzyżowym (około 20%) lub piersiowym (około 18%) [2].

Wiadomo, że wada powstaje we wczesnym etapie życia płodowego (21–28 dzień), jednak jak dotychczas nie wykazano jednoznacznie jej przyczyny.

Aktualnie uważa się, że jednym z najistotniejszych czynników jest niedobór kwasu foliowego w organizmie matki przed ciążą i w czasie jej trwania. Genetyczną komponentę ocenia się na około 60–70% na modelach mysich, jednakże obecność niewielu z tych genów potwierdzono u człowieka, chociaż opisywane są przypadki rodzinnego występowania wady. Uważa się, że ryzyko urodzenia drugiego dziecka z wadą wynosi 4%, a wzrasta do 10% w przypadku urodzenia dwojga dzieci z tą wadą [4]. Inne czynniki zwiększające ryzyko urodzenia dziecka z przepukliną oponowo-rdzeniową to zażywanie leków przeciwdrgawkowych, cukrzyca, nikotynizm, alkoholizm a także otyłość [5, 6].

Wada rozszczepowa kręgosłupa występuję na różnych poziomach i przyjmuje różne postacie o różnym stopniu zaawansowania.

Niezamknięcie łuków kręgowych prowadzi do powstania postaci tylnej wady, natomiast brak spojenia trzonów kręgów skutkuje postacią przednią wady. Postać przednia wady występuje bardzo rzadko i zwykle współistnieje z innymi wadami, a objawy rozszczepu kręgosłupa nie dominują w obrazie klinicznym.

Rozszczepione łuki kręgów oraz nieprawidłowo zrulonizowany rdzeń kręgowy mogą być pokryte oponami oraz warstwą mięśniowo-powięziową i skórą. Jest to zamknięta postać wady. Wówczas rdzeń kręgowy oraz pokrywające go opony nie są przemieszczone poza rozszczepiony kanał kręgowy (*spina bifida ocullta*) (Ryc 1A).

Jeżeli pod mięśniami i skórą znajdują się przemieszczone poza rozszczepione łuki kręgów opony, a nieprawidłowo zrulonizowany rdzeń kręgowy pozostaje nieprzemieszczony poza rozszczepiony kanał kręgowy, mamy do czynienia z przepukliną oponową zamkniętą (*meningocele ocullta*).

Z kolei gdy pod mięśniami i skórą znajdują się przemieszczone poza rozszczepione łuki kręgów opony oraz nieprawidłowo zrulonizowany rdzeń kręgowy, mówi się o przepuklinie oponowo-rdzeniowej zamkniętej (*myelomeningocele oculta*).

Wymienione powyżej trzy postacie zamknięte tej wady mogą występować pod postacią wady otwartej. Wówczas nieprawidłowo zrulonizowany rdzeń kręgowy oraz nieprawidłowo zamknięte opony pozostające w rozszczepionym kanale kręgowym nie są pokryte warstwą mięśniowo-powięziową oraz skórą (*spina bifida aperta , myeloschisis*).

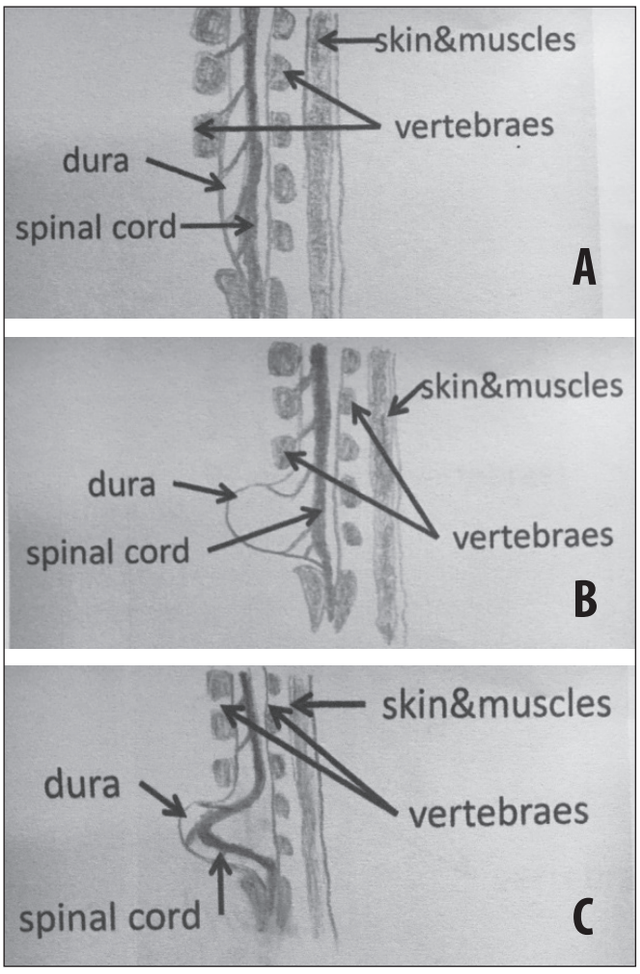
Kiedy poza niespojone łuki kręgów wydostają się niepokryte mięśniami i skórą opony, które mogą zawierać elementy nerwów rdzeniowych, a nieprawidłowo zrulonizowany rdzeń kręgowy pozostaje w rozszczepionym kanale kręgowym, mówimy o przepuklinie oponowej otwartej (*meningocele aperta*) (Ryc 1B).

Jeżeli poza niespojone łuki kręgowe przemieszczone są niepokryte mięśniami i skórą zarówno opony, jak i rozszczepiona płytka nerwowa i nerwy rdzeniowe, mówimy o przepuklinie oponowo-rdzeniowej otwartej (*myelomeningocele aperta*) (Ryc 1C).

Postaciom zamkniętym nierzadko towarzyszą tłuszczaki, zmiany na skórze w postaci przebarwień, jak np. plama mongolska, naczyniaki, znamiona czy zatoka włosowata.

Rozszczep przedni kręgosłupa może przyjmować takie same odmiany, jak postać tylna (*myeloschisis anterior, meningocele anterior, myelomeningocele anterior*) (Ryc. 2A-C).

W przypadku przepukliny oponowej przedniej i oponowo-rdzeniowej przedniej opony i elementy nerwowe zostają przemieszczone poza rozszczepiony odcinek kręgosłupa do przestrzeni zaotrzewnowej.



Ryc. 2. Przepuklina oponowo-rdzeniowa- postać przednia wady
A. przepuklina oponowo-rdzeniowa zamknięta;
B. przepuklina oponowa otwarta;
C. przepuklina oponowo-rdzeniowa otwarta.

Konsekwencją przepukliny oponowo-rdzeniowej jest porażenie neuromotoryczne obwodowo od poziomu uszkodzenia. Nasilenie objawów patologicznych związane jest nie tylko z poziomem uszkodzenia, ale głównie z postacią wady.[6]

Pierwszy dokładny opis wady zawdzięczamy szwajcarskiemu anatomowi i lekarzowi Gasparowi Bauhinowi (1560-1624). Obowiązującą do dziś nazwę łacińską: *spina bifida* wprowadził żyjący w tym samym czasie holenderski anatom i lekarz Nicolas Tulp (1593-1674), on też najprawdopodobniej jako pierwszy próbował wykonać chirurgiczną korekcję wady.

ROZPOZNANIE I LECZENIE WAD DYSRAFICZNYCH

Obecnie wady dysraficzne rozpoznawane są najczęściej podczas rutynowego badania ultrasonograficznego wykonywanego w drugim trymestrze ciąży. W przypadku rozległych wad możliwe jest ich rozpoznanie już podczas badania USG w pierwszym trymestrze ciąży. Stwierdzenie u płodu uwypuklenia lub nierównej linii grzbietu oraz nierównych obrysów kręgów może nasuwać podejrzenie wady dysraficznej. Ubytek kostny jest wykrywalny w około 80%, wady rdzenia kręgowego w około 50% (Ryc. 3).

Bez trudności można natomiast zobrazować wady mózgowia będące konsekwencją przepukliny oponowo-rdzeniowej. Należą do nich:

- wodogłowie – w przypadku poszerzenia rogów tylnych komór bocznych >8–10mm, (poszerzenie wymiarów rogów tylnych powyżej 15 mm określa się jako średni stopień, a powyżej 20 mm jako ciężki stopień wodogłowia;
- „objaw cytryny" – to spłaszczenie, a nawet wgłobienie kości czołowych powodujące zwężenie tej części czaszki względem części tylnej [7];
- „objaw banana" – przesunięcie struktur tylnego dołu czaszki do kanału kręgowego, co skutkuje wgłobieniem struktur tyłomózgowia. W wyniku tego móżdżek przybiera charakterystyczny kształt banana [8].

Objawy „cytryny" i „banana" najlepiej są widoczne do 24. tygodnia ciąży [8]. Później, na skutek narastania wodogłowia i wzrostu ciśnienia śródczaszkowego, a także dojrzewania i kostnienia kości czaszki, u większości płodów, stopniowo zanikają. Należy jednak pamiętać, że objaw cytryny nie jest jednak charakterystyczny tylko dla wad dysraficznych. Podczas prenatalnego badania USG w trakcie oceny struktur tylnego dołu czaszki ustala się stopień wgłobienia tyłomózgowia. Ocenie podlegają także: ruchomość kończyn dolnych oraz ewentualne wady stóp. Kolejne, kontrolne badania ultrasonograficzne pozwalają określić ewolucję zmian w OUN. Wszystkie te czynniki są podstawą do trójpunktowej oceny płodu z wadą rozszczepową kręgosłupa w obrazie USG (Tab. 1)[9].

W przypadku stwierdzenia wady dysraficznej u płodu, w celu doprecyzowania rozpoznania powinno zostać wykonane badanie rezonansu magnetycznego (MRI). Pozwala ono na dokładną ocenę tylnego dołu czaszki i określenie stopnia wgłobienia tylnojamowego oraz określenie górnego poziomu rozszczepu kręgosłupa, co może być przydatne w prognozowaniu poziomu uszkodzenia rdzenia kręgowego. Badanie to pozwala również precyzyjnie ocenić zawartość worka przepuklinowego oraz czy i w jakim zakresie jest on pokryty skórą. Wszystkie te informacje są niezbędne do zaplanowania sposobu leczenia (prenatalnego lub postnatalnego). Po przeprowadzonej interwencji chirurgicznej na otwartej macicy MRI jest metodą z wyboru w monitorowaniu skuteczności leczenia (Ryc 4).

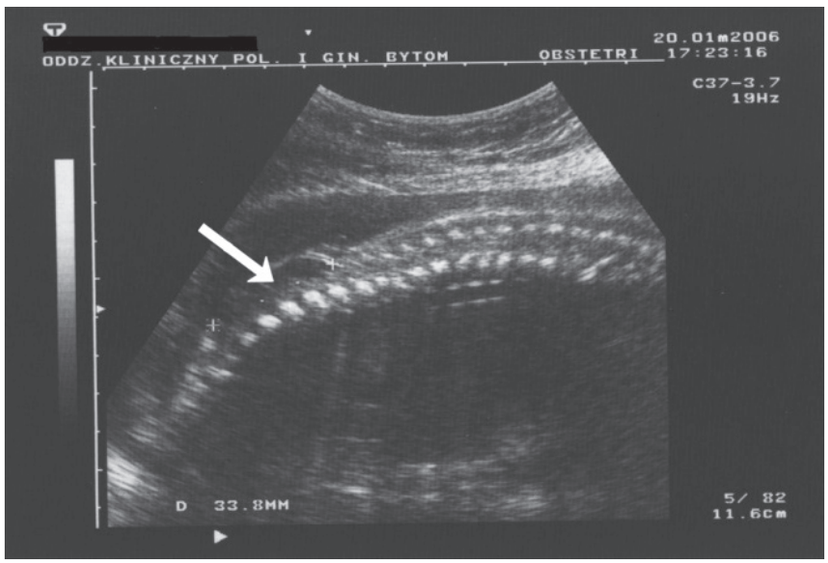
Współcześnie każdy noworodek urodzony z otwartą przepukliną oponowo-rdzeniową jest leczony operacyjnie w ciągu pierwszych 48 godzin życia.Chirurgiczne zaopatrzenie przepukliny oponowo-rdzeniowej polega na odcięciu worka przepuklinowego od otaczającej go skóry, następnie na wypreparowaniu opony twardej i, jeżeli warunki na to pozwalają na szczelnym zeszyciu jej ponad niezrulonizowaną płytką nerwową. Oponę należy bardzo delikatnie oddzielić od otaczających ją tkanek oraz uwolnić „we wrotach" przepukliny, to jest w miejscu gdzie zrasta się ona z rozszczepionym kanałem kręgowym, tak aby uzyskać uwolnienie

Tabela 1. Trójpunktowa oceny płodu

I punkt	Ocena OUN – cechy: objaw cytryny, banana, wentrykulomegalii, malformacji Chiariego II z określeniem stopnia wgłobienia tyłomózgowia
II punkt	Lokalizacja górnego poziomu uszkodzenia, definiowanego jako poziom kręgosłupa, przy którym rozejście się jąder kostnienia jest po raz pierwszy widoczne w serii „skanów"
III punkt	Obrazowanie kończyn dolnych w osi bocznej – 2 kości długie kończyny i pięta w tej samej projekcji; badanie w kierunku zmian deformacyjnych (koślawość, szpotawosc stopy)

Tabela 2. Kryteria kwalifikacji płodu do operacji prenatalnej.

Wskazania ze strony płodu	Przeciwskazania ze strony matki
Wiek ciążowy 21-26 Hbd	Ciąża bliźniacza, nawet jeśli oba płody dotknięte są wadą
Potwierdzony prawidłowy kariotyp	Infekcja wewnątrzmaciczna
Brak innych towarzyszących wad wrodzonych	Patologia łożyska oraz wystąpienie infekcji
Średnica komory bocznej <17 mm	Stwierdzenie czynności skurczowej mięśnia macicy maci
Górny poziom uszkodzenia MMC poniżej Th 1	BMI powyżej28
Potwierdzony w MRI zespół Arnolda Chiariego II (stopień II wgłobienia tylnojamowego)	Cukrzyca lub inne choroby metaboliczne
	Wiek ciężarnej poniżej 18 r.ż



Ryc. 3. Badanie USG płodu - widoczny rozszczep kręgosłupa w odcinku L-S.

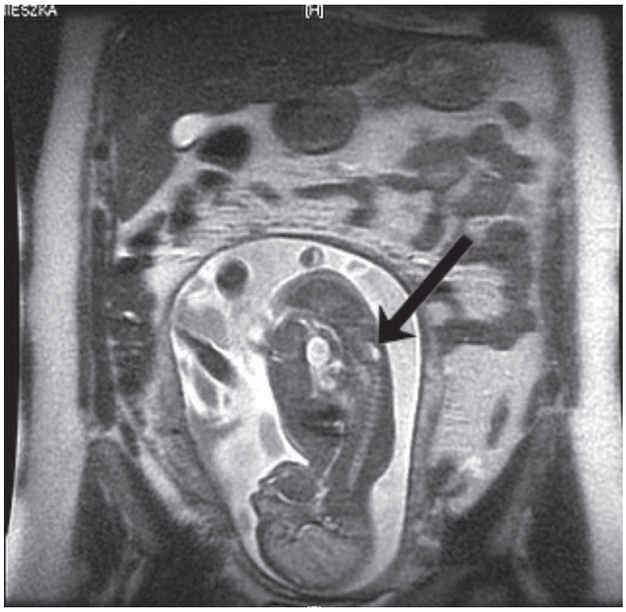
zakotwiczonego rdzenia dzięki czemu w znaczący sposób zmniejsza się ryzyko rozwoju wodogłowia.

Kolejne etapy operacji to pokrycie rozszczepionego kanału kręgowego warstwą mięśniowo-powięziową, a następnie skórą. W trakcie całego zabiegu należy zachować dużą ostrożność i precyzję celem zachowania jak największej liczby nieuszkodzonych naczyń i nerwów rdzeniowych.

Zgodnie z teorią podwójnego uderzenia Heffeza (*two hit theory*) zaburzenia związane z przepukliną oponowo-rdzeniową powstają w dwóch etapach. Pierwszy etap to nieprawidłowa rulonizacja rdzenia kręgowego w pierwszych tygodniach życia płodu. Drugi etap to wtórne uszkodzenie wynicowanego rdzenia kręgowego na skutek toksycznego działania płynu owodniowego oraz urazów mechanicznych rdzenia o ścianą macicy.

Badania przeprowadzone na modelu zwierzęcym w 1995 r. w wykazały, że wcześniejsze odseparowanie rdzenia kręgowego i nerwów rdzeniowych od toksycznego działania płynu owodniowego oraz mechanicznych urazów powoduje zmniejszenie się lub całkowite wycofanie zaburzeń neurologicznych z strony układu ruchu, moczowego i pokarmowego [10–12].

Wyniki brzmiały na tyle zachęcająco, że po żmudnych przygotowaniach i wnikliwej diagnostyce podjęto próbę



Ryc. 4. Badanie MRI płodu - widoczny rozszczep kręgosłupa w odcinku L-S.

zamknięcia przepukliny oponowo-rdzeniowej jeszcze w życiu płodowym. Pierwszą operację zamknięcia przepukliny oponowo-rdzeniowej drogą otwartej macicy wykonał J. Bruner w 1996 r, w Vanderbildt University, a od 1998 roku podjęto wykonywanie takich operacji w innych ośrodka, w tym w CHOP (*Children Hospital of Philadelphia)* [13]. Szeroka dyskusja na temat korzyści i ryzyka operacji płodowych przepukliny oponowo-rdzeniowej zdecydowały o przeprowadzeniu w Stanach Zjednoczonych randomizowanych badań. W trialu MOMS (*Myelomeningocele Study*) wzięły udział trzy amerykańskie ośrodki (Nshville, Philadelphia, San Francisco). W oparciu o wyniki trialu MOMS wykazano, że operacja płodowa MMC zmniejsza częstość występowania wodogłowia i poprawia funkcje motoryczne kończyn dolnych, jednak niesie ze sobą ryzyko porodu przedwczesnego i stwarza ryzyko dla matki [14, 15]. Wyniki przeprowadzonych 150 operacji w Śląskim Centrum Perinatologii, Ginekologii i Chirurgii Płodu w Bytomiu również potwierdzają te obserwacje.

Aktualnie prenatalne operacje przepukliny oponowo-rdzeniowej przeprowadzane są w kilku ośrodkach w Stanach Zjednoczonych, w Brazylii oraz w dwóch ośrodkach w Europie (Polska oraz Szwajcaria). Jednym ośrodkiem w Polsce gdzie przeprowadzane są operacje prenatalnego zamknięcia przepukliny oponowo-rdzeniowej drogą otwartej macicy (OFS – *Open Fetal Surgery*) jest Śląskie Centrum Perinatologii, Ginekologii i Chirurgii Płodu w Bytomiu. Operacje te wykonuje zespół lekarzy Śląskiego Uniwersytetu Medycznego w Katowicach: chirurdzy dziecięcy z Kliniki Chirurgii i Urologii Dziecięcej z Katowic oraz zespół ginekologów z Kliniki Ginekologii i Położnictwa w Bytomiu.

W czasie operacji przepukliny oponowo-rdzeniowej u płodu przeprowadzanej na otwartej macicy (OFS) wykonywane są te same procedury jak w czasie operacji MMC u noworodka, jednak ze względu na bardzo małe pole operacyjne i niezwykle delikatne tkanki płodu wymaga ona dużo większej precyzji i doświadczenia.

W kilku ośrodkach na świecie (Cincinati, Toronto, Barcelona) prowadzone są próby fetoskopowego zamknięcia przepukliny oponowo-rdzeniowej, które polegają na pokryciu rozszczepionego odcinka kanału kręgowego wypreparowaną skórą płodu. Operacje te obarczone są dużo większym ryzykiem powikłań i przede wszystkim nie obejmują one etapu odkotwiczenia rdzenia oraz nie zabezpieczają ubytku w kanale kręgowym warstwą mięśniową co zwiększa ryzyko wtórnego mechanicznego uszkodzenia rdzenia kręgowego w przyszłości.

Stosowane w czasie zabiegu fetoskopowego wszywanie łat gorateksowych na rozszczepiony kanał kręgowy zostało zarzucone przez wszystkie wiodące ośrodki zajmujące cię chirurgią MMC płodu ze względu na nieskuteczność tej metody i bardzo duże ryzyko ciężkich powikłań.

Nie każdy płód z rozpoznaną prenatalnie przepukliną oponowo-rdzeniową kwalifikuje się do operacji prenatalnej. Przeciwskazania do operacji prenatalnej mogą istnieć zarówno ze strony płodu, jak matki

Płody do operacji kwalifikowane są według ściśle określonych kryteriów (tzw Kryteria Johnsona) (Tab. 2) [16]:

Należy jednak z całą stanowczością podkreślić, że chociaż operacja prenatalna przepukliny oponowo-rdzeniowej zmniejsza w istotny statystycznie sposób następstwa tej ciężkiej wady, dając dziecku szansę na lepszy rozwój i większą samodzielność, to jednak jest ona również obarczona ryzykiem przedwczesnego porodu i zgonu dziecka.

Analiza MOMs wykazała, że zamknięcie przepukliny oponowo-rdzeniowej w okresie prenatalnym dwukrotnie zmniejsza ryzyko wystąpienia zastawkozależnego wodogłowia u dziecka, z 82% u dzieci operowanych po urodzeniu do 40 % w grupie dzieci operowanych w życiu płodowym. Takie wyniki zostały również przedstawione przez grupę z Polski, gdzie potrzeba założenia zastawki z powodu wodogłowia objęła zaledwie 28% dzieci operowanych prenatalnie i 80% operowanych postnatalnie. Zmniejszenie w przyszłości częstości występowania wodogłowia wiąże się również ze zmniejszeniem ryzyka wystąpienia komplikacji związanych z założeniem zastawki, takich jak: niedrożność drenu dokomorowego lub obwodowego, niesprawność mechaniczna samej zastawki oraz powikłania ze strony jamy otrzewnej [14, 15].

Zdolność do samodzielnego poruszania się jest traktowana przez większość dzieci z MMC oraz ich rodziców jako jeden z najważniejszych elementów poprawiających jakość ich życia. Analizy pacjentów operowanych w ośrodkach amerykańskich i polskim wykazały istotną statystycznie lepszą funkcję kończyn dolnych w wieku 30 miesięcy u dzieci operowanych prenatalnie w stosunku do grupy dzieci operowanych postnatalnie [14, 15].

Analiza biomechaniczna parametrów chodu pacjentów operowanych w naszym ośrodku wykazała lepszą stabilność i ruchomość w stawach biodrowych i skokowych u dzieci operowanych prenatalnie, co w istotny sposób zwiększa ich

szanse na samodzielne poruszanie.[17] Umiejętność samodzielnego poruszania się daje dziecku szansę na osiągnięcie większej samodzielności i niezależności w przyszłości.

Od czasu wprowadzenia operacyjnego zamknięcia rozszczepu kręgosłupa oraz wprowadzenia zastawek celem leczenia wodogłowia pojawiło się kolejne powikłanie, którym jest pęcherz i jelito neurogenne Nieprawidłowe unerwienie pęcherza moczowego powoduje poważne zaburzenia jego funkcji, uniemożliwiające utrzymanie prawidłowego ciśnienia w pęcherzu moczowym oraz jego regularne opróżnianie. Nieprawidłowe unerwienie pęcherza moczowego jest zawsze powiązane z odcinkowym, nieprawidłowym unerwieniem jelita, co w konsekwencji prowadzi do występowania przewlekłych zaparć (bladder and bowel syndrom).[18]

Analiza przeprowadzona u pacjentów operowanych prenatalnie i postnatalnie z powodu przepukliny oponowo-rdzeniowej w naszym materiale wykazała, że dzieci operowane prenatalnie wykazują w sposób istotny statystycznie mają lepsze socjalne trzymanie moczu, mniej zakażeń układu moczowego oraz, również w sposób istotny statystycznie, rzadziej cierpią z powodu zaparć.[19]

Wyniki badań przeprowadzonych w latach 2000-2012 porównujące czynność dolnych dróg moczowych u dzieci operowanych prenatalnie i postnatalnie z powodu MMC nie były zbyt zachęcające. Jednak badania te obejmowały głównie ocenę badania urodynamicznego, w którym, bez względu na ośrodek przeprowadzający prenatalną operację MMC wyniki były podobne. Dlatego wydaje się , że badanie urodynamiczne nie powinno stanowić jedynego kryterium oceny funkcji dolnych dróg moczowych.[20,21,22] Koh i współpracownicy w pracy z 2006 roku wykazali, że w analizowanych przez nich grupach dzieci, u których wykonano zamknięcie przepukliny oponowo-rdzeniowej w okresie prenatalnym częściej występowały objawy całkowitego odnerwienia zwieracza zewnętrznego cewki moczowej[23]

W analizowanym przez nas materiale nie potwierdziliśmy takich obserwacji. Lepsze socjalne trzymanie moczu u pacjentów operowanych prenatalnie można tłumaczyć lepiej zachowanymi funkcjami mięśni poprzecznie prążkowanych w tym mięśni przepony moczowo-płciowej , głównie mięśnia zwieracza zewnętrznego cewki moczowej.

Jednak na czynność dolnych dróg moczowych wydaje się mieć wpływ nie tylko czas przeprowadzenia zamknięcia przepukliny oponowo-rdzeniowej ale także wczesne włączenie zintegrowanej profilaktyki powikłań ze strony dolnych dróg moczowych tj. CIC i leków antycholinergicznych u wszystkich pacjentów operowanych z powodu MMC.

Wielu autorów podkreśla także istotnie statystycznie mniejszą liczbę zakażeń układu moczowego u pacjentów operowanych prenatalnie w stosunku do pacjentów operowanych postnatalnie. [24,25]. W badaniach przeprowadzonych w naszym ośrodku udowodniono również statystycznie rzadszą częstość występowania zaparć u pacjentów operowanych prenatalnie w stosunku do tych operowanych po urodzeniu. Te dwa fakty pozostają ze sobą spójne, ponieważ jest wiadomym, że występowanie zaparć zwiększa ryzyko infekcji w układzie moczowym ze względu na utrudnienie całkowitego opróżniania pęcherza moczowego co prowadzi do występowania przewlekłego zalegania moczu w pęcherzu. Brak regularnego i całkowitego opróżniania pęcherza moczowego stanowi jeden z najbardziej istotnych czynników ryzyka występowania zakażeń układu moczowego.

Obecność zaparć jest również złym czynnikiem prognostycznym utrzymania suchości socjalnej. Takie obserwacje potwierdzają badacze z wielu wiodących ośrodków. Dzieci operowane prenatalnie częściej uzyskują suchość socjalną ponieważ znacznie rzadziej cierpią z powodu zaparć.[26,27]

Istotna statystycznie mniejsza częstość występowania zaparć u dzieci operowanych prenatalnie z powodu MMC może być wynikiem zachowania dłuższego odcinka prawidłowo unerwionego jelita grubego.

Wiadomo, że zarówno ośrodkowy jak i obwodowy układ nerwowy płodów i noworodków charakteryzują się bardzo dużą możliwością reorganizacji szlaków nerwowych oraz ich dużą plastycznością co stwarza znacznie większe możliwości regeneracyjne zwłaszcza u płodów. [28]

Wydaje się więc prawdopodobne, że wcześniejsze odseparowanie rdzenia kręgowego i nerwów rdzeniowych od toksycznego działania płynu owodniowego oraz bezpośrednich urazów mechanicznych związanych z ruchami płodu w macicy pozwala na zachowanie większej liczby prawidłowo funkcjonujących szlaków neuronalnych oraz na powstawanie nowych. Zachowanie większej liczby prawidłowo funkcjonujących szlaków neuronalnych daje dziecku szansę na lepszą funkcję układów moczowego, pokarmowego i ruchu w przyszłości.

PODSUMOWANIE

Prenatalna operacja przepukliny oponowo-rdzeniowej dzięki skróceniu czasu ekspozycji rdzenia kręgowego i nerwów rdzeniowych na toksyczne działanie płynu owodniowego oraz ekspozycji na urazy mechaniczne zwiększa szansę na poprawę funkcji układów ruchu, moczowego i pokarmowego, dzięki czemu w sposób istotny statystycznie poprawia jakość życia dzieci z rozszczepem kręgosłupa.

PIŚMIENNICTWO

1. Sadler TW. Embryology of Neural Tube Deveopment. Am J Med Genet C Semin Med Genet. 2005;135:2-8
2. Cope H, McMahon K, Heise E, et al. Outcome and life satisfaction of adults with myelomeningocele. Disabil Health J. 2013;3:236-43.
3. Stone AR. Neurourologic evaluation and urologic management of spinal dysraphism. Neurosurg Clin N Am. 1995;2:269-77. Review.
4. Chen G, Liao L. Sacral neuromodulation for neurogenic bladder and bowel dysfunction with multiple symptoms secondary to spinal cord disease. Spinal Cord. 2014;16:45-49
5. Grewal J, Carmichael SL, Ma C et al. Maternal periconceptional smoking and alcohol consumption and risk for select congenital anomalies. Birth Defects Res A Clin Mol Teratol. 2008;82:519-26
6. Hüsler MR, Danzer E, Johnson MP et al. Prenatal diagnosis and postnatal outcome of fetal spinal defects with- out Arnold-Chiari II malformation. Prenat. Diagn. 2009;11: 1050-1732

7. Thomas M. The lemon sign. Radiology. 2003;228:206
8. Nicolaides KH, Campbell S, Gabbe SG et al. Ultrasound screening for spina bifida: cranial and cerebellar signs. Lancet. 1986;2:72-74
9. Herman-Sucharska I, Bożek P, Bryll A. Wady rozszczepowe kręgosłupa od diagnostyki do terapii Przegląd Lekarski. 2013;5:344-350
10. Silen U. Bladder function in healthy nenonates and its development during infancy. J Urol 2001; 166:2376-2381
11. Mueli M, Mueli-Simmen C, Hutchins GM, et eal. The spinal cord lesion in human fetus with myelomeningocele: Implications for fetal surgery. J Pediatr Surg. 1997;32:448-452.
12. Bouchard S, Davey MG, Rintoul NE, et al Correction of hindbrain hernation and anatomy of the vermis after in utero repair of myelomeningocele in sheep. J Pediatr Surg.2003;38:451-458.
13. Adzick NS, Sutton LN, Crombleholme TM, Flake AW. Successful fetal surgery for spina bifida. Lancet. 1998; 352:1675-1676.
14. Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011; 364:993-1004.
15. Zamłyński J, Olejek A, Koszutski T, et al. Comparsion of prenatal and postnatal treatments of spina bifida in Poland- a non-randomized, single–center study. J Matern Fetal Neonatal Med. 2014;27(14):1409-1417
16. Johnson MP, Sutton LN, Rintoul N et al. Fetal meningomyelocele repair: short term clinical outcomes. Am J Obstet Gynecol. 2003;189: 482-7.
17. Jochymczyk-Woźniak K, Michnik R, Nowakowska K et al. The long- therm effects of surgery in patients with myelomeningocele and their influence on parameters of gait- preeliminary research. Information Technology in Biomedicine , 2018;PP:602-611 ,DOI: 10.1007/978-3-319-91211-0_53
18. Cameron AP, Rodriguez GM, Gursky A et al. The Severity of Bowel Dysfunction in Patients with Neurogenic Bladder J Urol. 2015;194(5):1336-1341.
19. Pastuszka A, Bohosiewicz J, Koszutski T. Prenatal myelomeningocele repair improves urinary continence and reduces the risk of constipation. Neurourol Urodyn. 2018;37:2792-2798.
20. Macedo A Jr, Leal M, Rondon A, Ortiz V, Moron AF et al. Urological evaluation of patients that had undergone in utero myelomeningocele closure: a prospective assessment at first presentation and early follow-up. Do their bladder benefit from it? Neurourol Urodyn. 2015; 34:461-464
21. Clayton DB, Tanaka ST, Trusler L et al. Long-term urological impact of fetal myelomyeninocele closure. J Urol.2011;186(4 Suppl):1581-1585.
22. HoltzbelereinJ, Pope JC IV, Adams MC et al. The urodynamic profile of myelodysplasia in childhood spinal closure during gestation. J Urol. 2000;164:1336-1339.
23. Koh CJ, DeFilippo RE, Borer JG et al. Bladder and external urethral sphincter function after prenatal closure of myelomeningocele. J Urol. 2006;176:2232-2236.
24. Horst M, Mazzone L, Schraner T, Bodmer C, Mohrlen U, Mueli M, Gobert R. Prenatal myelomeningocele repair: Do bladders better? Neurourol Urodyn. 2016;9999:1-8
25. Brock JW,III, Carr MC, Adzick NS et al. Bladder function after fetal surgery for myelomeningocele. Pediatrics. 2015; 136:e906-e913
26. Müller T, Arbeiter K, Aufricht C. Renal function in meningomyelocele: risk factors, chronic renal failure, renal replacement therapy and transplantation. Curr Opin Urol. 2002; 12:479
27. Marshall DF, Boston VE. Does the absence of anal reflexes guarantee a "safe bladder" in children with spina bifida? Eur J Pediatr Surg. 2001;11 Suppl 1:S2
28. Nguyen HT, Benson CB, Bromley B et al. Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilatation (UTD)classification system). J Pediatr Urol. 2014;10:982-998

Zachęcamy wszystkich lekarzy, którzy wysunęli podejrzenie wady dysraficznej u płodu do przesłania pacjentki do Śląskiego Centrum Perinatologii, Ginekologii i Chirurgii Płodu w Bytomiu, gdzie zostanie przeprowadzona dalsza szczegółowa diagnostyka oraz będą przedstawione możliwe warianty leczenia takiej wady. Zwracamy również uwagę na fakt , że operacja prenatalnego zamknięcia przepukliny oponowo-rzdzeniowej u płodu nie może być przeprowadzona po 26. tygodniu ciąży, dlatego prosimy o kierowanie Pacjentek w jak najwcześniejszym tygodniu ciąży.

Konflikt interesów:
Wszyscy autorzy deklarują brak konfliktu interesów

AUTOR KORESPONDUJĄCY

Agnieszka Pastuszka
Górnośląskie Centrum Zdrowia Dziecka w Katowicach,
Oddział Chirurgii i Urologii Dziecięcej
ul. Medyków 16, 40-752 Katowice
tel: +48 694 413 617
32 2071750
e-mail: pastuszkowa@hotmail.com

Nadesłano: 13.02.2019
Zaakceptowano: 18.03.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

PONOWNE PRZYJĘCIE NA ODDZIAŁ INTENSYWNEJ TERAPII – EPIDEMIOLOGIA, PREDYKCJA I SKUTKI KLINICZNE

READMISSION TO THE INTENSIVE CARE UNIT - EPIDEMIOLOGY, PREDICTION AND CLINICAL CONSEQUENCES

Marek Grochla, Wojciech Saucha, Jarosław Borkowski, Piotr Knapik
ODDZIAŁ KLINICZNY KARDIOANESTEZJI I INTENSYWNEJ TERAPII, ŚLĄSKIE CENTRUM CHORÓB SERCA W ZABRZU, KATEDRA ANESTEZJOLOGII, INTENSYWNEJ TERAPII I MEDYCYNY RATUNKOWEJ, WYDZIAŁ LEKARSKI Z ODDZIAŁEM LEKARSKO-DENTYSTYCZNYM W ZABRZU, ŚLĄSKI UNIWERSYTET MEDYCZNY W KATOWICACH, ZABRZE, POLSKA

STRESZCZENIE

Ponowne przyjęcie pacjenta na oddział intensywnej terapii (rehospitalizacja) jest uważane za poważne zdarzenie niepożądane. Konsekwencje medyczne i ekonomiczne tego powikłania są na tyle istotne, iż odsetek rehospitalizacji na oddziale intensywnej terapii jest dziś uważany za wskaźnik świadczący o jakości funkcjonowania tych jednostek. W niniejszej pracy dokonano analizy dostępnego piśmiennictwa dotyczącego epidemiologii, predykcji i skutków klinicznych rehospitalizacji na oddziałach intensywnej terapii. Okazuje się, że w piśmiennictwie polskim brakuje prac dotyczących tego zagadnienia. Z danych pochodzących z innych krajów wynika, że odsetek rehospitalizacji zależy od wielu czynników i może wynosić od 2% do 15%, czas hospitalizacji po ponownym przyjęciu jest dłuższy, a śmiertelność szpitalna jest wyższa. Nie posiadamy też wiarygodnych narzędzi służących do predykcji tego powikłania. W polskim systemie ochrony zdrowia wieloprofilowe oddziały prowadzone są przez specjalistów w dziedzinie anestezjologii i intensywnej terapii. Pacjenci wypisywani z tych oddziałów stanowią populację istotnie podwyższonego ryzyka, z którą mogą się zetknąć lekarze reprezentujący różne dziedziny medycyny. Nieliczne dostępne dane wskazują, iż odległe wyniki leczenia pacjentów wypisywanych z oddziału intensywnej terapii w Polsce są bardzo złe, szczególnie u chorych w wieku podeszłym. Problem utrzymania właściwej ciągłości opieki po wypisie z oddziału zapewniającego wysoki poziom nadzoru nad pacjentem jest więc bardzo istotny dla zapewnienia koordynowanej opieki medycznej.

SŁOWA KLUCZOWE: rehospitalizacja, oddział intensywnej terapii, epidemiologia, predykcja

ABSTRACT

Readmission to the ICU is considered a serious adverse event. The medical and economic impact of this complication is so significant, that a percentage of ICU readmissions is today considered an indicator of ICU quality. This review paper analyzes the available literature on epidemiology, prediction and the clinical effects of ICU readmissions. It turns out that there are no publications on this subject in the Polish literature. Data from other countries indicate, that a percentage of ICU readmissions depends on a variety of factors and is ranging from 2% to 15%. Hospitalization time after ICU readmission is longer and hospital mortality is higher. We do not have reliable tools for the prediction of this complication. In the Polish healthcare system, multidisciplinary ICUs are run by specialists in anaesthesiology and intensive therapy. Patients discharged from these departments constitute a high-risk population and are further referred to doctors representing various medical specialities. Few available data indicate that long-term outcomes of patients discharged from Polish ICU are very bad, especially in the elderly. The problem of maintaining proper continuity of treatment after discharge from a high level of medical supervision is therefore very important to ensure coordinated medical care.

KEY WORDS: rehospitalisation, ICU, epidemiology, prediction

Wiad Lek 2019, 72, 7, 1387-1396

WSTĘP

Ponowne przyjęcie pacjenta na oddział intensywnej terapii (rehospitalizacja) jest poważnym zdarzeniem niepożądanym, które może znacząco wpłynąć na dalsze losy chorego. Konsekwencje tego powikłania są na tyle istotne, iż odsetek rehospitalizacji na oddziale intensywnej terapii jest dziś uważany za wskaźnik świadczący o jakości funkcjonowania danego oddziału [1, 2]. Wydaje się, że jest to spore uproszczenie, ponieważ na odsetek i przyczyny rehospitalizacji może wpływać również niska jakość opieki na innych oddziałach szpitalnych, czynniki związane ze stanem pacjenta przy wypisie, a także śmiertelność ogólna obserwowana na konkretnym oddziale intensywnej terapii podczas pierwotnego przyjęcia [3].

Rozważania dotyczące rehospitalizacji na oddziałach intensywnej terapii nie mogą być też oderwane od specyfiki ich funkcjonowania w określonym systemie ochrony zdrowia [4]. Różnice w tym zakresie pomiędzy różnymi systemami opieki zdrowotnej w obrębie samej tylko Europy mogą być bardzo znaczące [5]. Wiadomo, że nieskorygo-

wane wskaźniki śmiertelności nie są dobrym wskaźnikiem, świadczącym o jakości opieki na oddziałach intensywnej terapii [6]. Wobec takich uwarunkowań wszelkie analizy porównawcze dotyczące tego zagadnienia są znacznie utrudnione.

Oddziały intensywnej terapii zajmują szczególne miejsce w każdym systemie opieki zdrowotnej. Są one najlepiej przygotowane do leczenia pacjentów w stanach bezpośredniego zagrożenia życia. Wyposażone w wysokospecjalistyczny i kosztowny sprzęt, zapewniają najwyższe wskaźniki liczby personelu medycznego przypadającego na jednego pacjenta, w porównaniu do innych oddziałów szpitalnych [7, 8]. Pacjenci przyjmowani są na oddziały intensywnej terapii na ogół w bardzo ciężkim stanie ogólnym, a inwazyjność stosowanych procedur wiąże się z koniecznością zastosowania specjalistycznej aparatury monitorującej. Z tych wszystkich względów oddziały te generują najwyższe koszty w procesie stacjonarnego leczenia w każdym szpitalu, niezależnie od jego profilu. O skali tego problemu może świadczyć fakt, iż w 2013 roku w samych tylko Stanach Zjednoczonych połowa chorych z rozpoznaną sepsą wymagała leczenia w warunkach oddziału intensywnej terapii [9, 10].

Obserwowane obecnie zwiększanie się liczby stanowisk na oddziałach intensywnej terapii jest spowodowane między innymi szybkim starzeniem się społeczeństwa, a więc jest to trend o zasięgu globalnym. Wiadomo też, że pełne zaspokojenie potrzeb zdrowotnych społeczeństwa w tym zakresie nie jest już dziś możliwe i nie będzie też możliwe w przyszłości [11]. Problemem wielu krajów (w tym Polski) jest zbyt mała liczba oddziałów i stanowisk intensywnej terapii w stosunku do liczby pozostałych łóżek szpitalnych [11, 12].

W polskim systemie ochrony zdrowia wieloprofilowe oddziały prowadzone są wyłącznie przez specjalistów w dziedzinie anestezjologii i intensywnej terapii i noszą nazwę oddziałów anestezjologii i intensywnej terapii. Nie jest to jednak rozwiązanie uniwersalne. W innych krajach intensywną terapią zajmują się także lekarze reprezentujący różne dziedziny medycyny, a wiele oddziałów ma charakter monodyscyplinarny [13, 14]. Różnorodne ścieżki kariery i wyjściowe przygotowanie zawodowe lekarzy zajmujących się intensywną terapią wskazują na konieczność ujednolicenia szkolenia podyplomowego. Znakomitym przykładem takiej inicjatywy jest program CoBaTrICE wprowadzony przez ESICM (*European Society of Intensive Care Medicine*) w 2006 roku [15]. Program ten został zaadoptowany i wprowadzony do obowiązującego programu specjalizacji w dziedzinie anestezjologii i intensywnej terapii w Polsce.

Różnice w funkcjonowaniu oddziałów intensywnej terapii w różnych krajach mogą być bardzo znaczące. Wynika to z różnej roli, jaką pełnią te oddziały w różnych systemach opieki zdrowotnej. W wielu krajach oprócz pacjentów w stanach zagrożenia życia na oddziałach tych hospitalizowani są również chorzy po poważniejszych rutynowych zabiegach operacyjnych [16]. Niezależnie od lokalnych uwarunkowań należy również pamiętać, że główna przyczyna przyjęcia pacjenta na oddział intensywnej terapii zależy także od profilu danego szpitala, ponieważ istotny odsetek przyjęć na stanowiska intensywnej terapii dokonuje się zawsze z terenu macierzystej jednostki. W niektórych szpitalach na oddziale intensywnej terapii będą więc dominowali chorzy z chorobami układu krążenia, w innych pacjenci z powikłaniami choroby nowotworowych, a w jeszcze innych – pacjenci po rozległych urazach [17–19]. Jest to kolejny czynnik ogromnie utrudniający prowadzenie analiz porównawczych pomiędzy oddziałami, które mogą funkcjonować w zupełnie różnych warunkach.

Z analizy większości prac analizujących losy pacjentów rehospitalizowanych na oddziale intensywnej terapii wypływa wniosek, iż podczas kolejnej hospitalizacji pacjenci ci przebywają na oddziale dłużej, a ich śmiertelność jest istotnie wyższa. Przyczyny gorszych wyników leczenia u chorych rehospitalizowanych są niewątpliwie złożone. Niektórzy autorzy uważają, że wynika to z kolonizacji i przebytych infekcji patogenami wieloopornymi, chwiejnej wydolności ważnych dla życia narządów oraz osłabienia wynikającego z uprzedniego długotrwałego unieruchomienia [20].

Pacjenci wypisywani z oddziałów intensywnej terapii trafiają później na oddziały o bardzo różnym profilu, pod opiekę lekarzy reprezentujących różne dziedziny medycyny. Problem zachowania ciągłości opieki po wypisie z oddziału zapewniającego wysoki poziom opieki nad pacjentem jest więc bardzo istotny. Od niedawna wiadomo, że odległe wyniki leczenia pacjentów wypisywanych z oddziału intensywnej terapii w Polsce są złe, szczególnie u chorych w wieku podeszłym [21]. Z analizy dostępnego piśmiennictwa (które będzie szczegółowo analizowane w dalszych częściach pracy) wynika, że w innych krajach czas hospitalizacji po ponownym przyjęciu do OIT jest zwykle dłuższy, a śmiertelność szpitalna u tych chorych jest wyższa. Nie wiadomo jednak, jak przedstawia się sytuacja w Polsce, ponieważ zagadnienia związane z ponownym przyjęciem na oddział intensywnej terapii nie były dotąd nigdy szczegółowo analizowane w piśmiennictwie polskim. Jedyne opublikowane dotąd prace na ten temat dotyczyły chorych rehospitalizowanych po uprzednio wykonanych operacjach kardiochirurgicznych w monospecjalistycznych oddziałach intensywnej terapii [17, 22], tymczasem wiadomo, że w Polsce dominują dziś oddziały intensywnej terapii o profilu ogólnym [23].

Podsumowując, chorzy wypisywani z oddziałów intensywnej terapii stanowią populację istotnie podwyższonego ryzyka, z którą mogą się zetknąć lekarze pracujący na różnego rodzaju oddziałach o profilu zarówno zabiegowym jak i niezabiegowym.

REHOSPITALIZACJE PACJENTÓW WYPISYWANYCH Z ODDZIAŁÓW INTENSYWNEJ TERAPII O RÓŻNYM PROFILU

CHIRURGICZNE ODDZIAŁY INTENSYWNEJ TERAPII (SURGICAL ICU)

Na oddziały intensywnej terapii o profilu chirurgicznym (zabiegowym) przyjmowani są pacjenci po różnego rodzaju

procedurach chirurgicznych. Przeważają w nich chorzy po operacjach planowych, trafiający do obszaru intensywnej terapii z uwagi na istotne obciążenia zdrowotne i konieczność stosowania inwazyjnego monitorowania w okresie pooperacyjnym. Niezależnie od zabiegu operacyjnego, od którego rozpoczyna się wtedy proces leczenia, oddziały te mogą dodatkowo grupować pacjentów po konkretnych operacjach, w związku z czym nabierają one jeszcze bardziej monospecjalistycznego charakteru – co przyczynia się również do mniejszej heterogenności analizowanej populacji. Jest możliwe, że dlatego większość prac analizujących problem rehospitalizacji na oddziałach intensywnej terapii pochodzi właśnie z oddziałów o profilu zabiegowym.

Pierwszą, wysoce specyficzną grupą monodyscyplinarnych, zabiegowych oddziałów intensywnej terapii stanowią kardiochirurgiczne oddziały pooperacyjne. Z uwagi na fakt, iż zdecydowana większość pacjentów po operacjach kardiochirurgicznych wymaga wentylacji mechanicznej i inwazyjnego monitorowania, chorzy trafiają tam bezpośrednio po wykonanej operacji. Większość chorych po uzyskaniu stabilizacji przekazywana jest do dalszego leczenia na oddziale kardiochirurgii.

W pracy van Diepen i wsp. [24] przeanalizowano 10 799 przyjęć na pooperacyjne oddziały intensywnej terapii o profilu kardiochirurgicznym w Kanadzie. Współczynnik rehospitalizacji wyniósł 4,4%, a pacjenci przyjmowani ponownie charakteryzowali się znacznie dłuższym czasem hospitalizacji (średnio 19,9 dnia przy średniej wynoszącej 3,3 dnia w pozostałej grupie) oraz wielokrotnie wyższą śmiertelnością (14,4% przy 2,2% u pozostałych chorych). W grupie chorych rehospitalizowanych istotnie częściej występowały też wszelkiego rodzaju powikłania pooperacyjne [24].

Kolejne dwie prace dotyczące rehospitalizacji na kardiochirurgicznych oddziałach intensywnej terapii pochodzą z ośrodków polskich. Jarząbek i wsp. [17] przeanalizowali 2 076 chorych hospitalizowanych w ośrodku poznańskim, a Litwinowicz i wsp. [22] – 10 992 chorych leczonych w ośrodku krakowskim. Uzyskane wyniki były zbliżone, choć generalnie odsetek rehospitalizacji w polskich ośrodkach był nieco niższy niż w badaniu kanadyjskim (odpowiednio 2,7% i 1,8%), jednak śmiertelność wśród chorych ponownie przyjmowanych do OIT była jeszcze wyższa (odpowiednio: 26,8% i 23,9%).

Analizowana dotychczas seria prac pochodzi z lat 2014–2015, a analizowany materiał – z jeszcze wcześniejszego okresu, tymczasem wiadomo że w kardiochirurgii charakterystyka operowanej populacji zmienia się bardzo dynamicznie. W tej sytuacji przeanalizowano również te prace, które ukazały się w ciągu ostatnich dwóch lat. I tak na przykład Lee i wsp. [25] przeanalizowali 4 869 chorych operowanych w jednym ośrodku na terenie Wielkiej Brytanii. Chorzy wymagający ponownego przyjęcia do obszaru intensywnej terapii stanowili 3,2%, a ich śmiertelność była nadal bardzo wysoka (18% przy 3,2% w pozostałej populacji). Jeszcze wyższy odsetek rehospitalizacji przedstawiono w opublikowanej w 2019 roku pracy Li i wsp. [26] (6,3%), jednak analizowano w niej wyłącznie populację poddaną operacjom zastawek serca. Różnica w śmiertelności pomiędzy pacjentami rehospitalizowanymi a pozostałą populacją była w tej grupie również znacząca (odpowiednio 22,5% i 1,8%).

W podsumowaniu tej części można stwierdzić, że odsetek chorych wymagających ponownego przyjęcia na oddział intensywnej terapii jest wśród chorych po operacjach kardiochirurgicznych w miarę stały i oscyluje w granicach 2–4%. Ponowne przyjęcie wiąże się ze znacznie wyższą śmiertelnością, zawierającą się w przedziale 15–25%. Główne przyczyny ponownego przyjęcia na oddział intensywnej terapii to niestabilność hemodynamiczna, niewydolność oddechowa i różnego rodzaju powikłania pooperacyjne [17, 22].

Kolejna część rozważań dotyczyć będzie pacjentów po różnego rodzaju operacjach niekardiochirurgicznych, hospitalizowanych na oddziałach intensywnej terapii. W odróżnieniu od chorych po operacjach kardiochirurgicznych, pacjenci ci stanowią mało homogenną grupę. Niektórzy z nich przyjmowani są na oddziały intensywnej terapii planowo (podobnie jak chorzy po operacjach kardiochirurgicznych), jednak istotna część tych przyjęć dokonuje się w trybie pilnym z powodu wystąpienia powikłań okołooperacyjnych. Powikłania zdarzają się po każdej operacji, jednak wiadomo, że najczęściej występują one po rozległych i obciążających procedurach naczyniowych, neurochirurgicznych, torakochirurgicznych, a także po poważnych operacjach onkologicznych związanych z rozległą resekcją tkanek lub narządów [27, 28]. Coraz częściej do takich operacji kwalifikowani są też chorzy w wieku starszym, z licznymi dodatkowymi schorzeniami. Jeszcze inną kategorię stanowią chorzy hospitalizowani na oddziale intensywnej terapii po zabiegach operacyjnych będących konsekwencją ciężkich urazów (szczególnie urazów wielonarządowych) [19, 29].

Wydaje się, że wskaźniki związane z odsetkami rehospitalizacji na oddziale intensywnej terapii u pacjentów po różnego rodzaju operacjach zmieniają się dynamicznie w związku z rozwojem intensywnej terapii i coraz skuteczniejszą predykcją poważnych powikłań pooperacyjnych. Kilkanaście lat temu ponowne przyjęcia na oddział intensywnej terapii o profilu chirurgicznym były stosunkowo częste. W pracy Timmers i wsp. [27] analizującej dane pochodzące z lat 1995–2000 wskazano, że wśród chorych przyjmowanych na chirurgiczny oddział intensywnej terapii po różnego rodzaju operacjach, odsetek ponownych przyjęć wynosił 8%. Odsetek chorych przyjmowanych ponownie był zróżnicowany w zależności od rodzaju wykonanego uprzednio zabiegu operacyjnego i pozostawał najwyższy po rozległych operacjach brzusznych i naczyniowych (odpowiednio 14% i 10%). W pracy Kaben i wsp. [30] (pochodzącej z tego samego okresu czasu) odsetek chorych rehospitalizowanych był jeszcze wyższy, co piąty pacjent wymagał ponownego przyjęcia na oddział intensywnej terapii podczas swojej hospitalizacji. W obu cytowanych pracach podkreślano, że leczenie tych chorych zdecydowanie częściej kończyło się niepowodzeniem.

Znacznie lepsze wyniki pojawiają się w pracach publikowanych współcześnie. W pracy pochodzącej z 2019

roku, w której przeanalizowano dane 1 445 chorych przyjmowanych na chirurgiczny oddział intensywnej terapii w Cleveland Clinic w Stanach Zjednoczonych, odsetek ponownych przyjęć wyniósł zaledwie 5,5%. Śmiertelność pacjentów przyjmowanych ponownie była jednak nadal pięciokrotnie wyższa niż w pozostałej populacji, tak więc prawidłowość polegająca na gorszych wynikach leczenia u chorych rehospitalizowanych obserwuje się również we współczesnej medycynie okołooperacyjnej [31].

Podobny do cytowanego powyżej odsetek rehospitalizacji obserwowano również u chorych hospitalizowanych w oddziale intensywnej terapii z powodu rozległych urazów. W pracy Fakhry i wsp. [29] odsetek chorych przyjmowanych ponownie wyniósł 4,5%, a śmiertelność w tej grupie wyniosła aż 19,3%. Warto zauważyć, że ponad 70% chorych przyjmowanych ponownie wymagało przyjęcia do 72 godzin od pierwotnego wypisu.

Duży uraz dla organizmu chorego stanowią też rozległe operacje torakochirurgiczne, a chorzy po takich zabiegach są często planowo przyjmowani na oddział intensywnej terapii o profilu chirurgicznym. W ostatnio opublikowanej pracy przeanalizowano 1874 wypisów chorych po rozległej resekcji płuca z oddziału intensywnej terapii, stwierdzając, że ponownego przyjęcia wymagało zaledwie 3,3% chorych, natomiast śmiertelność w tej populacji osiągnęła 25,4%. Wystąpienie zespołu niewydolności oddechowej dorosłych i majaczenie pooperacyjne okazały się niezależnymi czynnikami mającymi wpływ na śmiertelność wewnątrzszpitalną u chorych w tej szczególnej grupie [28].

W pracy wieloośrodkowej pochodzącej z 2010 roku, przeanalizowano retrospektywnie 753 pacjentów, leczonych w warunkach oddziału intensywnej terapii po poważnych operacjach neurochirurgicznych. Ogółem, 7,7% chorych wymagało ponownego przyjęcia na oddział intensywnej terapii a śmiertelność w tej populacji wyniosła 15,5%. Pacjenci rehospitalizowani byli bardziej zagrożeni zgonem, a punktacja w skali APACHE II była u nich istotnie wyższa niż w pozostałej populacji, i to zarówno przy pierwszym, jak i przy ponownym przyjęciu [25].

Podsumowując można stwierdzić, że pacjenci rehospitalizowani na oddziałach intensywnej terapii o profilu zabiegowym są bardziej obciążeni zdrowotnie i charakteryzują się powikłanym przebiegiem pooperacyjnym. Wielochorobowość osób starszych oraz ich znacznie mniejsze rezerwy życiowe w sposób naturalny predysponują tych chorych do ponownego przyjęcia. Potwierdza się fakt, że śmiertelność pacjentów ponownie hospitalizowanych na oddziale intensywnej terapii jest znacznie wyższa w porównaniu do pacjentów przebywających podczas swojej hospitalizacji tylko jeden raz na takim oddziale. Powikłania pooperacyjne są nieco odmienne w każdej z dziedzin chirurgii, jednak niektóre z nich powtarzają się, niezależnie od rodzaju wykonanej operacji. Uważa się, że główne przyczyny ponownego przyjęcia do obszaru intensywnej terapii to niewydolność oddechowa, zaostrzenie przewlekłej niewydolności krążenia i powikłania kardiologiczne, oraz sepsa [25–30].

NIEZABIEGOWE ODDZIAŁY INTENSYWNEJ TERAPII MEDYCZNE (MEDICAL ICU)

W niektórych systemach opieki zdrowotnej chorzy leczeni chirurgicznie i zachowawczo hospitalizowani są na odrębnych oddziałach intensywnej terapii. Pomimo to, niełatwo jest natrafić na dane pochodzące z oddziałów intensywnej terapii o profilu czysto medycznym.

W jednej z najczęściej cytowanych, klasycznych publikacji dotyczącej rehospitalizacji, autorstwa Rosenberg i wsp. [32] przeanalizowano dane 4 684 chorych przyjętych na oddział intensywnej terapii o profilu medycznym w Stanach Zjednoczonych na przestrzeni kolejnych 5 lat. Odsetek ponownych przyjęć wyniósł 9,6%. Autorzy wskazali, że połowa chorych wymagających rehospitalizacji powracała na oddział intensywnej terapii w ciągu 72 godzin. Śmiertelność u rehospitalizowanych pacjentów była znacznie wyższa niż w pozostałej populacji (odpowiednio 43% i 8%), przy dwukrotnie dłuższym średnim czasie pobytu podczas ponownego pobytu na oddziale intensywnej terapii. Dane nie napawają optymizmem, jednak należy pamiętać, że praca ta została opublikowana w 2001 roku [32].

W innej, nowszej pracy badano możliwości predykcji rehospitalizacji na grupie 5 293 chorych hospitalizowanych na medycznych oddziałach intensywnej terapii. Okazało się, że skumulowany odsetek rehospitalizacji do 24 godzin wyniósł 2%, a do 7 dni – około 7% [33]. Większość chorych hospitalizowana była ponownie do 72 godzin od wypisu [33].

Specyficzną grupą chorych wymagających przyjęć na medyczne oddziały intensywnej terapii stanowią pacjenci z chorobami nowotworowymi. W badaniu przeprowadzonym w 2019 roku przeanalizowano losy 691 takich chorych po wypisie z oddziału intensywnej terapii. Rehospitalizowani chorzy zostali podzieleni na trzy grupy w zależności od czasu wypisu z oddziału: do 2 dni, od 2 do 7 dni i powyżej 7 dnia. Z analizy wykluczono chorych, których wypisano z oddziału intensywnej terapii do innego szpitala oraz chorych, u których *a priori* zadecydowano o ograniczeniu leczenia do paliatywnego (wykluczając tym samym ponowne przyjęcie do obszaru wzmożonego nadzoru). W tak szczególnej grupie ponownego przyjęcia wymagało aż 25,8% chorych. Połowa rehospitalizowanych pacjentów została przyjęta z powodu niewydolności oddechowej i sepsy. Śmiertelność ogólna na medycznym oddziale intensywnej terapii leczącym pacjentów onkologicznych wyniosła około 24% i u chorych rehospitalizowanych wcale nie była znacząco wyższa (30%) [18].

Reasumując, w piśmiennictwie medycznym można spotkać bardzo zróżnicowane informacje dotyczące rehospitalizacji na oddziałach intensywnej terapii, a dane z oddziałów o profilu czysto medycznym nie są żadnym wyjątkiem. Co ciekawe, wyższa śmiertelność podczas pierwotnego pobytu na oddziale intensywnej terapii (taka jak obserwowana na oddziałach leczących pacjentów onkologicznych) nie wiązała się wcale z proporcjonalnie wyższą śmiertelnością po przyjęciu takich chorych ponownie do obszaru intensywnej terapii [18, 32].

WIELOPROFILOWE ODDZIAŁY INTENSYWNEJ TERAPII (GENERAL ICU)

Wieloprofilowe oddziały intensywnej terapii (grupujące zarówno pacjentów po wykonanych operacjach, jak i hospitalizowanych z innych przyczyn) są najczęściej spotykane we wszystkich systemach ochrony zdrowia. W Polsce oddziały takie są prowadzone wyłącznie przez specjalistów w dziedzinie anestezjologii i intensywnej terapii. W naszym kraju funkcjonuje obecnie 398 wieloprofilowych oddziałów anestezjologii i intensywnej terapii, dysponujących łącznie 2799 stanowiskami [23]. Odsetek rehospitalizacji na tych oddziałach jest nieznany. Ze względu na te uwarunkowania, informacje dotyczące oddziałów intensywnej terapii o profilu ogólnym pochodzące z innych krajów wydają się najistotniejsze do naszych dalszych rozważań.

Z zacytowanej wcześniej pracy Weigl i wsp. [23] wynika jednak kilka dodatkowych wniosków. Okazuje się, że w Polsce zaledwie 2% wszystkich łóżek szpitalnych stanowią stanowiska intensywnej terapii, co po przeliczeniu daje wskaźnik około 7 stanowisk na 100 000 mieszkańców. W analizowanym przez autorów 2012 roku hospitalizowano na tych stanowiskach 48 282 pacjentów dorosłych, a śmiertelność w tej populacji wyniosła 42%. Wynika z tego, że 15% wszystkich zgonów pacjentów w polskich szpitalach dokonywało się właśnie na stanowiskach wieloprofilowych oddziałów intensywnej terapii. Autorzy wskazali, że niższą śmiertelność obserwowano na oddziałach anestezjologii i intensywnej terapii III stopnia referencyjności, zlokalizowanych często w jednostkach uniwersyteckich oraz w instytutach badawczych. Według autorów korzyści odnosili chorzy leczeni na tych oddziałach, w których pielęgniarka prowadziła maksymalnie dwóch chorych [23].

Uwarunkowania te bardzo trudno przenieść w obszar wieloprofilowych oddziałów intensywnej terapii, zlokalizowanych w innych systemach opieki zdrowotnej. Lai i wsp. [34] przeanalizowali dane ponad 192 000 chorych hospitalizowanych w 2006 roku na wszystkich oddziałach intensywnej terapii o profilu ogólnym na Tajwanie. Okazało się, że aż 13% chorych wymagało ponownego przyjęcia do OIT w okresie obserwacji, a nieomal połowę wszystkich rehospitalizowanych stanowili pacjenci powyżej 68. roku życia [34]. Po kilku latach w tym samym kraju przeanalizowano ponad 650 000 chorych wypisanych z oddziału intensywnej terapii po pobycie, który wymagał zastosowania wentylacji mechanicznej w procesie leczenia. Okazało się, że rehospitalizacji do 7 dni od wypisu wymagało znacznie mniej, bo tylko 4,5% pacjentów [35]. Chorzy byli na ogół przyjmowani ponownie na oddział z tą samą jednostką chorobową co podczas pierwotnego przyjęcia, a odsetek chorych powyżej 65. roku życia osiągnął aż 77%. Ponownie więc pojawia się tu prawidłowość, polegająca na niższym odsetku rehospitalizacji w nowszych badaniach. Zaskakuje to, że Chia-Chen i wsp. [35] wskazują na płeć męską jako czynnik predysponujący do rehospitalizacji, natomiast Lai i wsp. [34] wskazują na płeć żeńską jako bardziej predysponowaną [34].

W badaniu przeprowadzonym w 2011 roku w Danii analizowano ponad 38 000 wypisów z oddziałów intensywnej terapii o profilu ogólnym, z czego 2,9% chorych wymagało później rehospitalizacji w ciągu 48 godzin od pierwotnego wypisu. Śmiertelność szpitalna w całej leczonej na oddziale intensywnej terapii populacji wynosiła jednak 6,7%, w związku z czym trudno byłoby te dane odnieść do polskiej populacji [20].

Przeglądając piśmiennictwo, natrafiono też na dwie metaanalizy, które oparto się na łącznym materiale ponad 480 000 chorych [36, 37]. Oba artykuły wskazują jednoznacznie, że rehospitalizacja jest związana z wyższą śmiertelnością oraz z cięższym stanem klinicznym w momencie przyjęcia. Hosein i wsp. [37] wyliczyli, że na 100 pacjentów wypisywanych z oddziału intensywnej terapii, od czterech do sześciu pacjentów będzie prawdopodobnie ponownie przyjętych, a u trzech do siedmiu nastąpi zgon przed wypisem ze szpitala. Autorzy ci po raz pierwszy zwrócili też uwagę na fakt, iż w badaniach wykluczających ponowne przyjęcie na oddział intensywnej terapii u chorych z kwalifikacją do dalszego leczenia paliatywnego, współczynnik rehospitalizacji i zgonów na oddziale intensywnej terapii był istotnie niższy [37]. Wong i wsp. [36] wskazują natomiast, że średni współczynnik rehospitalizacji na oddziałach intensywnej terapii o profilu ogólnym wynosi około 5,7%. Udowodnili przy tym, że śmiertelność pacjentów rehospitalizowanych może wahać się w bardzo szerokich granicach (od 10% do ponad 50%), przy czym w pozostałej populacji może również zawierać się w bardzo szerokim przedziale (od 1% do 18%) [36].

Podsumowując można stwierdzić, że – podobnie jak w populacji chirurgicznej – główną grupę pacjentów wymagających ponownego przyjęcia na oddziały intensywnej terapii stanowią osoby starsze, z licznymi dodatkowymi obciążeniami zdrowotnymi, a najczęstszą przyczyną rehospitalizacji pozostają powikłania sercowo-naczyniowe, niewydolność oddechowa oraz sepsa [34, 35, 38]. Średni współczynnik rehospitalizacji w wieloprofilowych oddziałach intensywnej terapii wynosi około 6%. Chorzy rehospitalizowani stanowią więc sporą populację, charakteryzującą się znacznie wyższą śmiertelnością i kosztami leczenia, w stosunku do pozostałych leczonych na tych oddziałach chorych. Nie wiadomo, czy wskaźniki te okażą się zbliżone w warunkach polskich, ponieważ w naszym kraju nie prowadzono dotąd żadnych badań dotyczących tego zagadnienia.

PREDYKCJA REHOSPITALIZACJI NA ODDZIAŁACH INTENSYWNEJ TERAPII

W dotychczasowych rozważaniach zwracano już kilkakrotnie uwagę na fakt, iż ponowne przyjęcie do oddziału intensywnej terapii na ogół zwiększa śmiertelność i koszty leczenia [39, 40, 41]. Ponownego przyjęcia należy więc starać się uniknąć, planując wypis pacjenta z oddziału intensywnej terapii, tym bardziej że niski odsetek rehospitalizacji jest dziś uważany za wskaźnik świadczący o prawidłowym funkcjonowaniu oddziału intensywnej terapii [1, 3, 42]. Jest zrozumiałe, że wobec takich uwarunkowań predykcja powrotu pacjenta na oddział intensywnej tera-

pii stała się przedmiotem zainteresowania wielu badaczy, którzy próbowali analizować użyteczność różnych skal w przewidywaniu tego powikłania [3, 24, 26, 31, 38, 43–47]. Zastosowanie odpowiednich skal predykcyjnych mogłoby bowiem umożliwić klinicystom identyfikację tych chorych, których po prostu nie należy wypisywać przedwcześnie.

Informacje, które mogłyby posłużyć do skonstruowania skal predykcyjnych pojawiają się dość często w literaturze medycznej. Większość autorów, którzy w swoich pracach zajęli się analizą chorych przyjmowanych ponownie na oddział intensywnej terapii, próbowała identyfikować równocześnie niezależne czynniki ryzyka takiej rehospitalizacji [3, 26, 24, 31, 38, 43, 44–47]. Działanie takie jest stosunkowo proste, jeśli posiada się odpowiednio dużą bazę danych, w której zgromadzone zostały dane zarówno chorych, którzy po wypisie wymagali rehospitalizacji, jak i pozostałych pacjentów, którzy zostali wypisani z OIT i już nie powrócili. Teoretycznie można przyjąć, że na podstawie każdej takiej pracy można byłoby skonstruować skalę służącą do analizowania ryzyka rehospitalizacji w analizowanej populacji. Większość autorów zatrzymywała się jednak na etapie identyfikacji niezależnych czynników ryzyka, ponieważ zaproponowanie odpowiedniej skali wiąże się z koniecznością przeprowadzenia jej walidacji, co jest działaniem znacznie bardziej złożonym.

Nawet jeżeli prawdopodobieństwo jest zmienną o charakterze ciągłym, to i tak ostatecznym celem użycia skali predykcyjnej jest podjęcie na jej podstawie jednoznacznej decyzji, a więc działania o charakterze binarnym (tak lub nie). Rozważając wypis pacjenta z oddziału intensywnej terapii, podejmowana jest więc decyzja o zatrzymaniu chorego na oddziale lub o jego wypisie (*stay or go*) [3]. Znalezienie odpowiedniego rozwiązania jest jednak trudniejsze, niż mogłoby się to na pozór wydawać.

W 2008 roku Gajic i wsp. [48] zaproponowali skalę SWIFT (*Stability and Workload Index for Transfer*), która została utworzona na podstawie analizy stosunkowo niewielkiej populacji (1 131 chorych) hospitalizowanych na pojedynczym oddziale intensywnej terapii o profilu medycznym w Stanach Zjednoczonych na przełomie 2004 i 2005 roku. Skalę skonstruowano, określając niezależne czynniki ryzyka rehospitalizacji u 100 pacjentów, którzy wymagali ponownego przyjęcia na oddział intensywnej terapii. Skalę tę poddano następnie walidacji u 783 chorych leczonych później w tym samym ośrodku i u 708 chorych hospitalizowanych na oddziale intensywnej terapii o profilu ogólnym (medyczno-chirurgicznym) w Europie [48].

Wyniki tej pracy nie są szczególnie odkrywcze. Predykcja ponownego przyjęcia za pomocą opracowanej skali SWIFT była w obu walidowanych oddziałach (a więc różnych populacjach) umiarkowana i – co zrozumiałe – znacznie lepsza w ośrodku amerykańskim (w którym została pierwotnie utworzona). Zaletą tej skali pozostaje jednak prostota i łatwość przeprowadzanych obliczeń [48]. Punktacji podlegają takie zmienne jak: miejsce, z którego przyjmowano chorego do OIT, czas hospitalizacji, ostatni zmierzony współczynnik PaO_2/FiO_2, punktacja w skali GCS w chwili wypisu, oraz ostatni pomiar $paCO_2$ w gazometrii krwi tętniczej. W celu wyliczenia punktacji, należy dodać do siebie punktację uzyskaną w poszczególnych częściach skali (Tab. I).

Pomimo istotnych ograniczeń, na które zresztą wskazują sami autorzy, użyteczność skali SWIFT była później analizowana przez wielu badaczy. Być może wynika to z faktu, iż była to pierwsza zaproponowana skala predykcyjna tego rodzaju. W piśmiennictwie pojawiły się więc zarówno prace, które przedstawiają skalę SWIFT jako przydatną i użyteczną [38, 44], jak i takie, których wyniki negują sens jej stosowania w ogóle [3, 49]. Ofoma i wsp. [33] wykazali, że dołączenie rutynowej analizy skali SWIFT opóźniło moment wypisu z oddziału intensywnej terapii u jednej trzeciej pacjentów, co jednak pozostało bez wpływu na odsetek późniejszych rehospitalizacji [33].

Do predykcji rehospitalizacji w OIT próbowano również stosować skale, które oryginalnie zostały stworzone i zwalidowane do predykcji śmiertelności podczas pierwotnego przyjęcia do OIT (a więc do zupełnie innego celu), takie jak np. skala APACHE II (*Acute Physiology and Chronic Health Evaluation II*) czy skala SAPS II (*Simplfied Acute Physiology Score II*). Próbowano również zastosować do tego celu skalę SOFA (*Sequential Organ Failure Assessment*), służącą do oceny zaawansowania niewydolności wielonarządowej w przebiegu sepsy i skalę TISS-28 (*Therapeutic Intervention Scoring System*), oceniającą intensywność działań pielęgniarskich w oddziałach intensywnej terapii [3, 38, 44].

Woldhek i wsp. [3] wykazali, że pacjenci przyjmowani ponownie mieli wyższe punktacje w skalach APACHE II, SAPS II, SWIFT i SOFA. Wymienieni autorzy przeprowadzili swoje badania na dużej populacji 19 750 chorych, przyjmowanych na oddział intensywnej terapii na przestrzeni kolejnych 14 lat. Okazało się, że wszystkie analizowane modele predykcyjne charakteryzowały się polem pod krzywą nie przekraczającą wartości 0,7, a więc ich wartość dyskryminacyjna była co najwyżej umiarkowana [3]. Autorzy pracy przyjęli jednak arbitralnie, że użyteczność każdej z analizowanych przez nich skal predykcyjnych jest zadowalająca, jeżeli tylko pole pod krzywą (*Area Under Curve* – AUC) jest większe niż 0,6 [3]. Z takimi założeniami metodycznymi trudno się zgodzić, ponieważ punkt odcięcia wyznaczony za pomocą takiej krzywej nie ma wystarczającej zdolności różnicowania badanych grup i tym samym podejmowania decyzji o charakterze binarnym (*stay or go*). Zbliżone do poprzednich badaczy wyniki uzyskali również Rosa i wsp. [38], którzy analizowali użyteczność predykcyjną skal SWIFT, SOFA i TISS-28 w dniu wypisu. Na użyteczność skali SWIFT wskazują natomiast Kareliusson i wsp., [44] którzy udowodnili, że osiągnięcie 15 punktów w tej skali w dniu wypisu wiąże się z wyższym ryzykiem ponownego przyjęcia i 30-dniową śmiertelnością.

W predykcji rehospitalizacji próbowano także ocenić przydatność skali MEWS (*Modified Early Warning Score*) [44]. Skala ta powinna mieć spory potencjał predykcyjny, ponieważ analizuje proste parametry życiowe i jest stosowana powszechnie w pracy systemów wczesnego ostrzegania w szpitalach w krajach zachodnich (Tab. II)

Tabela I. Skala SWIFT.

Zmienna		Liczba punktów
Miejsce z którego przyjmowanego chorego do OIT	oddział ratunkowy / SOR	0
	inny oddział szpitalny / oddział opieki długoterminowej	8
Czas hospitalizacji w OIT (w dniach)	<2	0
	2-10	1
	>10	14
Ostatni zmierzony współczynnik $Pa0_2/FiO_2$	>400	0
	<400 i ≥150	5
	<150 i ≥100	10
	<100	13
Punktacja w skali GCS w chwili wypisu z OIT	>14	0
	11-14	6
	8-10	14
	<8	24
Ostatni pomiar $paCO_2$ w gazometrii krwi tętniczej	<45mmHg	0
	>45mmHg	5

Tabela II. Skala MEWS.

Liczba punktów	3	2	1	0	1	2	3
Skurczowe ciśnienie tętnicze (mmHg)	<70	71-80	81-100	101-199		>200	
Akcja serca (min^{-1})		<40	41-50	51-100	101-110	111-129	>130
Częstość oddechów (min^{-1})		<9		9-14	15-20	21-29	>30
Temperatura (°C)		<35		35-38,4		>38,5	
Reakcja na bodźce				pełna	na głos	na ból	brak

[50]. Punktacja w skali MEWS wyliczona w chwili wypisu pacjenta z OIT okazała się istotnie wyższa u pacjentów, którzy wymagali później rehospitalizacji (2,3±1,3 i 1,8±1,2, p=0,03). Niestety, autorzy nie ocenili w tej pracy pola pod krzywą i tym samym zdolności dyskryminacyjnej skali MEWS [44].

Innym interesującym narzędziem, które może służyć do predykcji rehospitalizacji na OIT jest tzw. indeks Rothmana (*Rothman Index),* który opiera się na ocenie 26 parametrów, takich jak funkcje życiowe, badania laboratoryjne, rytm serca i prace wykonywane przez zespół pielęgniarski. Indeks wylicza się odejmując od liczby 100 sumę wszystkich czynników ryzyka. U typowych chorych hospitalizowanych na oddziale medycznym lub zabiegowym punktacja ta mieści się na ogół w przedziale od zera do 100 punktów, natomiast w populacji chorych leczonych na OIT może osiągać wartości ujemne. Okazało się, że indeks ten sprawdza się znakomicie w predykcji zgonu w ciągu 24 godzin po przyjęciu do OIT (AUC>0,9), jednak nie ma szczególnej wartości w predykcji rehospitalizacji w OIT (AUC=0,62) [51]. Warto jednak zauważyć, że żaden chory nie wymagał ponownego przyjęcia do OIT w ciągu 48 godzin od wypisu, jeżeli indeks Rothmana był wyższy niż 83 punkty [31, 52].

Grupa badaczy z Francji postanowiła skonstruować własną skalę, którą otrzymała roboczą nazwę MIR Score (*Minimazing ICU Readmission)* (Tab. II). Skala ta została utworzona na podstawie analizy danych 3 462 chorych, wśród których około 3% wymagało ponownego przyjęcia lub zmarło do 7 dni od wypisu z OIT. W badanej populacji model ten okazał się znacznie dokładniejszy od testowanej równolegle przez autorów skali SAPS II i SWIFT [45]. W przeglądzie systematycznym opracowanym w 2013 roku przez Hosein i wsp. [53] wskazano na model MIR Score jako najbardziej obiecujący. Wadą tej skali jest konieczność zastosowania współczynnika β, którego obecność wymaga użycia automatycznych algorytmów podczas prowadzenia obliczeń [53].

Być może w ocenie ryzyka rehospitalizacji nie będzie już wkrótce konieczności tworzenia nowych skal, lecz będzie można wykorzystać w tym celu sztuczną inteligencję, a więc systemy komputerowe posiadające zdolność do interpretowania danych, nauki na ich podstawie, a następnie wykorzystania tej wiedzy po to, aby wykonywać określone zadania i cele. Wykazano już, że algorytmy sztucznej inteligencji potrafią dokładniej oszacować prawdopodobieństwo rehospitalizacji w porównaniu do skali SWIFT [43]. Za pomocą algorytmów sztucznej inteligencji można też

wcześniej przewidywać i rozpoznawać sepsę, co przekłada się na znaczącą poprawę wyników leczenia [54].

W przewidywaniu rehospitalizacji w OIT są więc stosowane (z mniejszym lub większym powodzeniem) różne skale predykcyjne. Niezależnie od tego, w nieomal każdej pracy poświęconej rehospitalizacji w OIT, autorzy dokonują próby identyfikacji niezależnych czynników ryzyka wystąpienia tego powikłania. Uzyskane wyniki są oczywiście w znacznym stopniu uzależnione od specyfiki danego oddziału, jednak pewne reguły pozostają niezmienne – ryzyko rehospitalizacji jest zawsze większe u chorych w starszym wieku, hospitalizowanych uprzednio na OIT z powodu sepsy lub niewydolności serca [17, 22, 24, 26, 27, 34]. Na kardiochirurgicznych oddziałach pooperacyjnych listę tych czynników należałoby jeszcze uzupełnić o uprzednio przebyte operacje wielozastawkowe i zabiegi złożone (polegające na połączeniu rewaskularyzacji naczyń wieńcowych z procedurą wymiany zastawek serca) [24, 26, 47]. Jeszcze inne dodatkowe niezależne czynniki ryzyka występują na niekardiochirurgicznych oddziałach intensywnej terapii o profilu zabiegowym, gdzie znaczenie mają również podwyższone wskaźniki zapalne w chwili wypisu [30], a także przebycie uprzednio zabiegu naczyniowego lub onkologicznego [27]. Udowodniono również, że niezależnym czynnikiem ryzyka rehospitalizacji jest przebycie incydentu majaczenia podczas pierwotnej hospitalizacji [28].

Reasumując, w literaturze medycznej znajduje się wiele różnorodnych, często mało użytecznych, sposobów identyfikacji chorych, u których prawdopodobieństwo rehospitalizacji na oddziale intensywnej terapii jest wyższe niż w pozostałej populacji hospitalizowanej na tym oddziale. Różnorodność uzyskiwanych przez poszczególnych badaczy wyników jest jednak tak duża, że w chwili obecnej trudno byłoby rekomendować do tego celu tę czy inną skalę. Wydaje się, że wobec takie różnorodności danych, najwłaściwszym sposobem predykcji jest w chwili obecnej tworzenie lokalnych skal predykcyjnych na podstawie własnych danych poszczególnych oddziałów. Należy oczekiwać, że w najbliższym czasie metoda ta zostanie zastąpiona przez komputerowe algorytmy oparte na sztucznej inteligencji. Warto w tym miejscu przypomnieć pewną regułę o charakterze fundamentalnym. Niezależnie od zastosowanej metody postępowania, zdolność przewidywania wszelkiego rodzaju powikłań zależy od utworzenia dużej i i dobrze funkcjonującej bazy danych w obrębie oddziału intensywnej terapii. Bez posiadania rzetelnej i regularnie aktualizowanej bazy danych żaden oddział nie jest dziś w stanie rzetelnie ocenić jakości swojej pracy, zauważyć pojawiających się problemów oraz przewidzieć, u których pacjentów mogą wystąpić groźne powikłania.

LOSY ODLEGŁE CHORYCH REHOSPITALIZOWANYCH NA OIT?

Wspomniano już, że pobyt na oddziale intensywnej terapii jest kosztowny, tak więc chorzy rehospitalizowani (którzy często wymagają kilkukrotnego pobytu i których czas pobytu na oddziale jest znacząco dłuższy) z pewnością generują wyjątkowo wysokie koszty dla każdego systemu opieki zdrowotnej. W tej sytuacji warto byłoby uzyskać wiedzę na temat finalnego efektu leczenia tych pacjentów, których wyjątkowo trudne i przedłużające się leczenie kończy się ostatecznie wypisem z oddziału intensywnej terapii. Interesujący byłby więc ich czas przeżycia, kolejne hospitalizacje (niekoniecznie na oddziale intensywnej terapii) oraz rzeczywista jakość życia po opuszczeniu oddziału i szpitala. Niestety, w dostępnym piśmennictwie nie istnieją praktycznie żadne publikacje dotyczące losów odległych pacjentów wymagających ponownego przyjęcia do oddziału intensywnej terapii. W tej sytuacji można jedynie przyjrzeć się dostępnym badaniom oceniającym całą wypisywaną z takich oddziałów populację (obejmującą oczywiście również chorych rehospitalizowanych).

W dużym, kanadyjskim badaniu analizowano retrospektywnie populację ponad 500 000 chorych wypisanych z grupy oddziałów intensywnej terapii w Kanadzie w latach 2002–2012 [55]. Pierwszorazowy pobyt na OIT przeżyło 84% pacjentów. Prawdopodobieństwo zgonu w obserwacji jednorocznej u chorych wypisanych ze szpitala wyniosło 11%, zaś prawdopodobieństwo zgonu w obserwacji pięcioletniej osiągnęło 29%. Warto podkreślić, że uzyskane wyniki w obserwacji odległej różniły się istotnie w różnych grupach wiekowych. Prawdopodobieństwo zgonu w obserwacji rocznej u chorych powyżej 75. roku życia wyniosło 17,5%, podczas gdy w młodszej grupie wyniosło zaledwie 6,8% [55].

W innej pracy tej samej grupy badawczej zawężono analizę wyłącznie do pacjentów wentylowanych mechanicznie przez ponad 21 dni [41]. Takie założenie przybliża znacząco uzyskane wyniki do realiów polskich oddziałów intensywnej terapii. Okazało się, że w populacji ponad 200.000 chorych takich pacjentów było zaledwie 11 594 (5,4%), jednak ich śmiertelność szpitalna wyniosła aż 42,4%. Prawdopodobieństwo zgonu w obserwacji rocznej wyniosło o tych chorych 11,5%, zaś w obserwacji pięcioletniej – 42,0% [41].

W brazylijskiej pracy opublikowanej w 2018 roku analizowano losy ponad 100 000. chorych hospitalizowanych na oddziale intensywnej terapii [56]. Prawdopodobieństwo zgonu w obserwacji jednorocznej wyniosło u tych chorych 25,5%. W analizie wieloczynnikowej wykazano, że częstość rehospitalizacji oraz zgonów była częstsza w populacji medycznej w porównaniu do populacji chirurgicznej [56].

Jak mają się te wyniki do dzisiejszej sytuacji w Polsce? Niezwykle trudno jest odpowiedzieć na to pytanie. Jedyne dostępne dane porównawcze zawarte są w pracy opublikowanej w 2016 roku, opartej na niewielkim materiale 870 chorych leczonych na wieloprofilowym oddziale anestezjologii i intensywnej terapii Śląskiego Centrum Chorób Serca w Zabrzu [21]. Celem tej pracy była ocena charakterystyki klinicznej i wyników leczenia pacjentów po 79. roku życia przyjmowanych na oddział intensywnej terapii oraz porównanie wyników uzyskanych w tej populacji do wyników pozostałych pacjentów leczonych w tym samym czasie na oddziale. W pracy tej analizowano jednak

również dane dotyczące dalszych losów każdego chorego po wypisie z oddziału intensywnej terapii. Uzyskane wyniki są szokujące i zupełnie odmienne od przedstawionych powyżej w pracach Hill i wsp. [55] oraz Lima i wsp. [56]

Pacjenci powyżej 79. roku życia stanowili 8,6% analizowanej populacji. Śmiertelność szpitalna była zbliżona w obu grupach i przekraczała 40%, jednak odległe wyniki leczenia w starszej grupie wiekowej okazały się fatalne. Nieomal połowa chorych zmarła do jednego miesiąca po wypisie (45,2%), a śmiertelność roczna według analizy Kaplana-Meiera wyniosła aż 82%. Sporą frustrację budzą zresztą także wyniki odległe uzyskane w młodszej grupie wiekowej, w której wskaźniki wynosiły te osiągnęły wartości odpowiednio 27,3% i 48% [21]. Budzi to głęboki niepokój i skłania do zastanowienia nad jakością i ciągłością opieki po wypisie z oddziałów intensywnej terapii w Polsce. Temat ten znakomicie wpisuje się w często obecnie dyskutowane zagadnienia związane z promowaniem koordynowanej opieki medycznej.

PIŚMIENNICTWO

1. Kramer AA, Higgins TL, Zimmerman JE. The association between ICU readmission rate and patient outcomes. Crit Care Med. 2013;41:24-33. doi: 10.1097/CCM.0b013e3182657b8a.
2. Maharaj R1, Terblanche M, Vlachos S. The Utility of ICU Readmission as a Quality Indicator and the Effect of Selection. Crit Care Med. 2018;46:749-756. doi: 10.1097/CCM.0000000000003002.
3. Woldhek AL, Rijkenberg S, Bosman RJ et al. Readmission of ICU patients: A quality indicator? J Crit Care. 2017;38:328-334. doi: 10.1016/j.jcrc.2016.12.001.
4. Prin M, Wunsch H. International comparisons of intensive care: informing outcomes and improving standards. Curr Opin Crit Care. 2012;18:700-706. doi: 10.1097/MCC.0b013e32835914d5.
5. Adamski J, Goraj R, Onichimowski D et al. The differences between two selected intensive care units located in central and northern Europe - preliminary observation. Anaesthesiol Intensive Ther. 2015;47:117-124. doi: 10.5603/AIT.a2015.0010.
6. Piechota M, Cywiński J, Piechota A et al. Is the unadjusted ICU mortality a good indicator of quality of ICU care? Intensive Care Med. 2018;44:127-128. doi: 10.1007/s00134-017-4903-0.
7. Kusza K, Piechota M. Wytyczne Polskiego Towarzystwa Anestezjologii i Intensywnej Terapii określające zasady kwalifikacji oraz kryteria przyjęcia chorych do Oddziałów Anestezjologii i Intensywnej Terapii. [download: 15.04.20019]; http://www.anestezjologia.org.pl/news,main,81.html
8. Nates JL, Nunnally M, Kleinpell R et al. A Framework to Enhance Clinical Operations, Development of Institutional Policies, and Further Research. Crit Care Med. 2016;44:1553-1602. doi: 10.1097/CCM.0000000000001856.
9. Keuffel EL, Stevens M, Gunnarsson C. A Monte Carlo simulation estimating US hospital cost reductions associated with hypotension control in septic ICU patients. J Med Econ. 2019;22:383-389. doi: 10.1080/13696998.2019.1576695.
10. Marino P. Intensywna terapia. 4th edn. Red pol. A. Kubler. Wrocław: Edra Urban & Partner; 2017.
11. Rhodes A, Ferdinande P, Flaatten H et al. The variability of critical care bed numbers in Europe. Intensive Care Med. 2012;38:1647-1653.
12. Wallace DJ, Seymour CW, Kahn JM. Hospital-level changes in adult ICU bed supply in the United States. Crit Care Med. 2017;45:e67-e76.
13. Bion J, Rothen HU. Models for intensive care training. A European perspective. Am J Respir Crit Care Med. 2014;189:256-262. doi: 10.1164/rccm.201311-2058CP.
14. Van Aken H, Mellin-Olsen J, Pelosi P. Intensive care medicine: a multidisciplinary approach! Eur J Anaesthesiol. 2011;28:313-315. doi: 10.1097/EJA.0b013e328345a441.
15. CoBaTrICE Collaboration. The educational environment for training in intensive care medicine: structures, processes, outcomes and challenges in the European region. Intensive Care Med. 2009;35:1575-1583. doi: 10.1007/s00134-009-1514-4.
16. Christiansen CF, Møller MH, Nielsen H et al. The Danish Intensive Care Database. Clin Epidemiol. 2016;8:525-530.
17. Jarząbek R, Bugajski P, Greberski K et al. Readmission to an intensive care unit after cardiac surgery: reasons and outcomes. Kardiol Pol. 2014;72:740-747. doi: 10.5603/KP.a2014.0062
18. Jeong BH, Na SJ, Lee DS et al. Readmission and hospital mortality after ICU discharge of critically ill cancer patients. PLoS One. 2019;14:e0211240. doi: 10.1371/journal.pone.0211240.
19. Michetti CP, Fakhry SM, Brasel K et al. Structure and Function of a Trauma Intensive Care Unit: a Report From the Trauma Icu Prevalence Project (TRIPP). J Trauma Acute Care Surg. 2019 Feb 7. doi: 10.1097/TA.0000000000002223. [Epub ahead of print].
20. van Sluisveld N, Bakhshi-Raiez F, de Keizer N et al. Variation in rates of ICU readmissions and post-ICU in-hospital mortality and their association with ICU discharge practices. BMC Health Serv Res. 2017;17:281. doi: 10.1186/s12913-017-2234-z.
21. Knapik M, Zbieralska E, Kłaczek B et al. Przebieg i wyniki leczenia pacjentów w wieku powyżej 79 lat hospitalizowanych na oddziale intensywnej terapii. Ann Acad Med Sile 2016;70:286–290.
22. Litwinowicz R, Bartus K, Drwila R et al. In-hospital mortality in cardiac surgery patients after readmission to the intensive care unit: a single-center experience with 10,992 patients. J Cardiothorac Vasc Anesth. 2015;29:570-575. doi: 10.1053/j.jvca.2015.01.029.
23. Weigl W, Adamski J, Goryński P et al. ICU mortality and variables associated with ICU survival in Poland: A nationwide database study. Eur J Anaesthesiol. 2018;35:949-954. doi: 10.1097/EJA.0000000000000889.
24. van Diepen S, Graham MM, Nagendran J et al. Predicting cardiovascular intensive care unit readmission after cardiac surgery: derivation and validation of the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) cardiovascular intensive care unit clinical prediction model from a registry cohort of 10,799 surgical cases. Crit Care. 2014;18:651. doi: 10.1186/s13054-014-0651-5.
25. Lee HF, Lin SC, Lu CL et al. Revised Acute Physiology and Chronic Health Evaluation score as a predictor of neurosurgery intensive care unit readmission: A case-controlled study. J Crit Care. 2010;25(2):294-9. doi: 10.1016/j.jcrc.2009.12.007.
26. Li S, Tang BY, Zhang B et al. Analysis of risk factors and establishment of a risk prediction model for cardiothoracic surgical intensive care unit readmission after heart valve surgery in China: A single-center study. Heart Lung. 2019;48:61-68. doi: 10.1016/j.hrtlng.2018.07.013.
27. Timmers TK, Verhofstad MH, Moons KG et al. Patients' characteristics associated with readmission to a surgical intensive care unit. Am J Crit Care. 2012;21:e120-8. doi: 10.4037/ajcc2012773.
28. Jung JJ, Cho JH, Hong TH et al. Intensive care unit (ICU) readmission after major lung resection: Prevalence, patterns, and mortality Thorac Cancer. 2017;8:33-39. doi: 10.1111/1759-7714.12406

29. Fakhry SM, Leon S, Derderian C et al. Intensive care unit bounce back in trauma patients: an analysis of unplanned returns to the intensive care unit. J Trauma Acute Care Surg. 2013;74:1528-33. doi: 10.1097/TA.0b013e31829247e7.
30. Kaben A, Corrêa F, Reinhart K et al. Readmission to a surgical intensive care unit: incidence, outcome and risk factors. Crit Care. 2008;12:R123. doi: 10.1186/cc7023.
31. Alarhayem AQ, Muir MT, Jenkins DJ, et al. Application of EMR-derived analytics in critical care: Rothman Index predicts mortality and readmissions in surgical ICU patients. J Trauma Acute Care Surg. 2019;86:635-641. doi: 10.1097/TA.0000000000002191.
32. Rosenberg AL, Hofer TP, Hayward RA et al. Who bounces back? Physiologic and other predictors of intensive care unit readmission. Crit Care Med. 2001;29:511-518.
33. Ofoma UR, Chandra S, Kashyap R et al. Findings from the implementation of a validated readmission predictive tool in the discharge workflow of a medical intensive care unit. Ann Am Thorac Soc. 2014;11:737-743. doi: 10.1513/AnnalsATS.201312-436OC.
34. Lai JI, Lin HY, Lai YC et al. Readmission to the intensive care unit: a population-based approach. J Formos Med Assoc. 2012;111:504-509. doi: 10.1016/j.jfma.2011.06.012..
35. Chu CC, Liu CJ, Shih CM, et al. The Risk and Related Factors for Readmission to an ICU Within 7 Days in Mechanically Ventilated Subjects - A Nationwide Population-Based Cohort Study Respir Care. 2015;60:1786-1795. doi: 10.4187/respcare.03868.
36. Wong EG, Parker AM, Leung DG et al. Association of severity of illness and intensive care unit readmission: A systematic review. Heart Lung. 2016;45:3-9.e2. doi: 10.1016/j.hrtlng.2015.10.040.
37. Hosein FS, Roberts DJ, Turin TC et al. A meta-analysis to derive literature-based benchmarks for readmission and hospital mortality after patient discharge from intensive care. Crit Care. 2014;18:715. doi: 10.1186/s13054-014-0715-6.
38. Rosa RG, Roehrig C, Oliveira RP et al. Comparison of Unplanned Intensive Care Unit Readmission Scores: A Prospective Cohort Study. PLoS One. 2015;10:e0143127. doi: 10.1371/journal.pone.0143127.
39. Hua M1, Gong MN, Brady J et al. Early and late unplanned rehospitalizations for survivors of critical illness. Crit Care Med. 2015;43:430-438. doi: 10.1097/CCM.0000000000000717.
40. Mourani PM, Kinsella JP, Clermont G, et al. Prolonged Outcomes after Nitric Oxide (PrONOx) Investigators. Intensive care unit readmission during childhood after preterm birth with respiratory failure. J Pediatr. 2014;164:749-755.e3. doi: 10.1016/j.jpeds.2013.11.062.
41. Hill AD, Fowler RA, Burns KE et al. Long-Term Outcomes and Health Care Utilization after Prolonged Mechanical Ventilation. Ann Am Thorac Soc. 2017;14:355-362. doi: 10.1513/AnnalsATS.201610-792OC
42. Boots RJ. Can readmissions really be used as an ICU performance indicator? Crit Care Med. 2013;41:331-332. doi: 10.1097/CCM.0b013e318270e20c.
43. Desautels T, Das R, Calvert J, et al. Prediction of early unplanned intensive care unit readmission in a UK tertiary care hospital: a cross-sectional machine learning approach. BMJ Open. 2017;7:e017199. doi: 10.1136/bmjopen-2017-017199.
44. Kareliusson F, De Geer L, Tibblin AO. Risk prediction of ICU readmission in a mixed surgical and medical population. J Intensive Care. 2015;3:30. doi: 10.1186/s40560-015-0096-1.
45. Ouanes I, Schwebel C, Français A, et al. A model to predict short-term death or readmission after intensive care unit discharge. J Crit Care. 2012;27:422.e1-9. doi: 10.1016/j.jcrc.2011.08.003.
46. Ponzoni CR, Corrêa TD, Filho RR et al. Readmission to the Intensive Care Unit: Incidence, Risk Factors, Resource Use and Outcomes: A Retrospective Cohort Study. Ann Am Thorac Soc. 2017;14:1312-1319. doi: 10.1513/AnnalsATS.201611-851OC.
47. Thomson R, Fletcher N, Valencia O et al. Readmission to the Intensive Care Unit Following Cardiac Surgery: A Derived and Validated Risk Prediction Model in 4,869 Patients. J Cardiothorac Vasc Anesth. 2018;32:2685-2691. doi: 10.1053/j.jvca.2018.04.033
48. Gajic O, Malinchoc M, Comfere TB et al. The Stability and Workload Index for Transfer score predicts unplanned intensive care unit patient readmission: initial development and validation. Crit Care Med. 2008;36:676-682. doi: 10.1097/CCM.0B013E318164E3B0.
49. Kastrup M, Powollik R, Balzer F et al. Predictive ability of the stability and workload index for transfer score to predict unplanned readmissions after ICU discharge. Crit Care Med. 2013;41:1608-15. doi: 10.1097/CCM.0b013e31828a217b.
50. Subbe CP, Davies RG, Williams E. Effect of introducing the Modified Early Warning score on clinical outcomes, cardio-pulmonary arrests and intensive care utilisation in acute medical admissions. Anaesthesia. 2003;58:797-802.
51. Rothman MJ, Rothman SI, Beals J 4th. Development and validation of a continuous measure of patient condition using the Electronic Medical Record. J Biomed Inform. 2013;46:837-848. doi: 10.1016/j.jbi.2013.06.011
52. Piper GL, Kaplan LJ, Maung AA et al. Using the Rothman index to predict early unplanned surgical intensive care unit readmissions. J Trauma Acute Care Surg. 2014;77:78-82. doi: 10.1097/TA.0000000000000265.
53. Hosein FS, Bobrovitz N, Berthelot S et al. A systematic review of tools for predicting severe adverse events following patient discharge from intensive care units. Crit Care. 2013;17:R102. doi: 10.1186/cc12747.
54. McCoy A, Das R. Reducing patient mortality, length of stay and readmissions through machine learning-based sepsis prediction in the emergency department, intensive care unit and hospital floor units. BMJ Open Qual. 2017;6:e000158. doi: 10.1136/bmjoq-2017-000158.
55. Hill AD, Fowler RA, Pinto R et al. Long-term outcomes and healthcare utilization following critical illness – a population-based study. Crit Care. 2016;20:76. doi: 10.1186/s13054-016-1248-y.
56. de Lima VCBF, Bierrenbach AL, Alencar GP, Increased risk of death and readmission after hospital discharge of critically ill patients in a developing country: a retrospective multicenter cohort study. Intensive Care Med. 2018;44(7):1090-1096. doi: 10.1007/s00134-018-5252-3.

Konflikt interesów:
Wszyscy autorzy deklarują brak konfliktu interesów.

AUTOR KORESPONDUJĄCY
Marek Grochla
Śląskie Centrum Chorób Serca w Zabrzu,
ul. M. Curie-Skłodowskiej 9,
41-800 Zabrze
e-mail: marek685@op.pl

Nadesłano: 15.04.2019
Zaakceptowano: 10.06.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

WYBRANE MECHANIZMY INDUKUJĄCE OPORNOŚĆ NA IMMUNOTERAPIĘ U CHORYCH NA RAKA JAJNIKA

SELECTED MECHANISMS INDUCING RESISTANCE TO IMMUNOTHERAPY IN PATIENTS WITH OVARIAN CANCER

Natalia Pietrzyk[1], Patrycja Piętak[1], Anna Pawłowska[1], Dorota Suszczyk[1], Agata Chudzik[1], Jan Kotarski[2], Iwona Wertel[1]
[1]PRACOWNIA IMMUNOLOGII NOWOTWORÓW, I KATEDRA I KLINIKA GINEKOLOGII ONKOLOGICZNEJ I GINEKOLOGII, UNIWERSYTET MEDYCZNY W LUBLINIE, LUBLIN, POLSKA
[2]I KATEDRA I KLINIKA GINEKOLOGII ONKOLOGICZNEJ I GINEKOLOGII, UNIWERSYTET MEDYCZNY W LUBLINIE, LUBLIN, POLSKA

STRESZCZENIE

W ostatnich latach obserwuje się intensywny rozwój terapii immunologicznych w leczeniu nowotworów złośliwych. Wśród badanych strategii leczenia znajdują się m.in. specyficzne przeciwciała monoklonalne, terapia adoptywna, a także szczepionki przeciwnowotworowe. Wiązane są duże nadzieje na wykorzystanie immunoterapii w leczeniu najbardziej złośliwych i śmiertelnych nowotworów, takich jak rak jajnika. Jednakże trwające badania wykazują jedynie nieznaczne wydłużenie przeżycia chorych. Jako możliwą przyczynę niepowodzenia wymienia się istnienie barier immunoterapii, które wynikają z niskiej immunogenności komórek raka jajnika, występowania zmienności mutacji, a także obecności specyficznego, immunosupresyjnego mikrośrodowiska nowotworowego, które ułatwia progresję nowotworu. W niniejszej pracy przedstawiono wybrane mechanizmy oporności nowotworów na terapię immunologiczną. W celu rozwoju skutecznych strategii leczenia ważne jest szczegółowe poznanie zarówno mechanizmów prowadzących do wystąpienia prawidłowej odpowiedzi na leczenie, jak i odpowiedzialnych za niepowodzenia terapeutyczne, wynikające z oporności na terapię.

SŁOWA KLUCZOWE: rak jajnika, immunoterapia, mechanizmy oporności, mikrośrodowisko nowotworowe

ABSTRACT

Recently, the intensive development of immunotherapies in the treatment of malignant tumors has been observed. The investigated treatment approaches including specific monoclonal antibodies, adoptive therapy and also anticancer vaccinations. The implementation of immunotherapy seems to be promising in treatment of the most malignant and fatal tumors including ovarian cancer. However, current findings have shown only a nonsignificant improvement of patients' survival. The possible cause of failure may be immunotherapy barriers that are a result of low immunogenicity level of ovarian cancer cells, mutation variability, and also the presence of a specific, immunosuppressive tumor microenvironment, which stimulates the cancer progression. The review presents the selected mechanisms of tumor resistance to immunological therapy. In order to project effective treatment approaches, it is necessary to understand both, mechanisms leading to the correct response for the treatment and causing therapeutic failures, resulting from resistance to therapy.

KEY WORDS: ovarian cancer, immunotherapy, resistance mechanisms, tumor microenvironment

Wiad Lek 2019, 72, 7, 1397-1402

WSTĘP

Rak jajnika (OC – *ovarian cancer*) cechuje się największą śmiertelnością wśród nowotworów złośliwych narządu rodnego kobiet. Pomimo agresywnych terapii, łączących leczenie chirurgiczne oraz adjuwantową chemioterapię, 5-letnie przeżycie w III i IV stopniu zaawansowania według Międzynarodowej Federacji Ginekologii i Położnictwa (FIGO – *International Federation of Gynecology and Obstetrics*) wynosi poniżej 25%. U ponad 80% pacjentek ostatecznie rozwija się oporność na leczenie chemioterapeutyczne [1]. Wyniki ostatnich badań klinicznych pokazują, że włączanie nowych leków, takich jak przeciwciała monoklonalne, nie powoduje statystycznie istotnego wydłużenia całkowitego przeżycia chorych. Dlatego projektowanie nowych terapii oraz poznanie przyczyn lekooporności jest bardzo istotne dla zwiększenia skuteczności terapii [1].

Spektakularne wyniki leczenia inhibitorami punktów kontrolnych uzyskano w czerniaku, raku nerki oraz niedrobnokomórkowym raku płuca, zaś wyniki w leczeniu OC są jedynie obiecujące. Prawdopodobnie jest to spowodowane barierami immunoterapii, do których zaliczamy niską immunogenność raka jajnika i zmienność mutacji (pojawianie się nowych mutacji i wariantów genetycznych opornych na rozpoznawanie przez układ immunologiczny). Ponadto, ekspresję wielu receptorów hamujących na limfocytach infiltrujących (TILs – *tumour-infiltrating lymphocytes*) raka jajnika, kompensacyjną ekspresję innych punktów kontroli, podczas gdy jeden z nich jest blokowany

oraz aktywność populacji immunosupresyjnych, takich jak: komórki T regulatorowe (Tregs), komórki supresyjne pochodzące z linii mieloidalnej (MDSCs – *myeloid-derived suppressor cells*) oraz makrofagi związane z nowotworem (TAMs – *tumour-associated macrophages*) [1].

W celu lepszego zrozumienia wpływu mikrośrodowiska nowotworowego na regulację odpowiedzi przeciwnowotworowej przeprowadzono liczne badania. Sato i wsp. [2] przeanalizowali zależność między obecnością TILs a całkowitym czasem przeżycia chorych na raka jajnika. Autorzy wykazali, że pacjentki z wysokim odsetkiem limfocytów T $CD8^+$ przeżywają średnio 55 miesięcy, natomiast niższy odsetek komórek $CD8^+$ wiąże się z krótszym czasem przeżycia, wynoszącym średnio 26 miesięcy [2]. Metaanaliza dziesięciu badań klinicznych przeprowadzona przez Hwang i wsp. [3] potwierdziła obserwację, że niższy odsetek TILs związany jest z krótszym przeżyciem chorych [1]. Pozwoliło to na wyciągnięcie wniosku, że immunoterapia nowotworów jest procesem wieloetapowym. W celu uzyskania optymalnej odpowiedzi immunologicznej należy zapewnić odpowiednią liczbę limfocytów T efektorowych, skutecznie rozpoznających specyficzne antygeny oraz mających zdolność migracji do środowiska nowotworowego, a także przełamania tolerancji immunologicznej i aktywnego działania przeciwnowotworowego [1].

NEGATYWNE REGULATORY ODPOWIEDZI IMMUNOLOGICZNEJ

Komórki nowotworowe wykorzystują także naturalnie występujące mechanizmy kontrolne układu immunologicznego, aby uniknąć odpowiedzi immunologicznej. Należą do nich immunologiczne punkty kontrolne (*immune-checkpoints*).

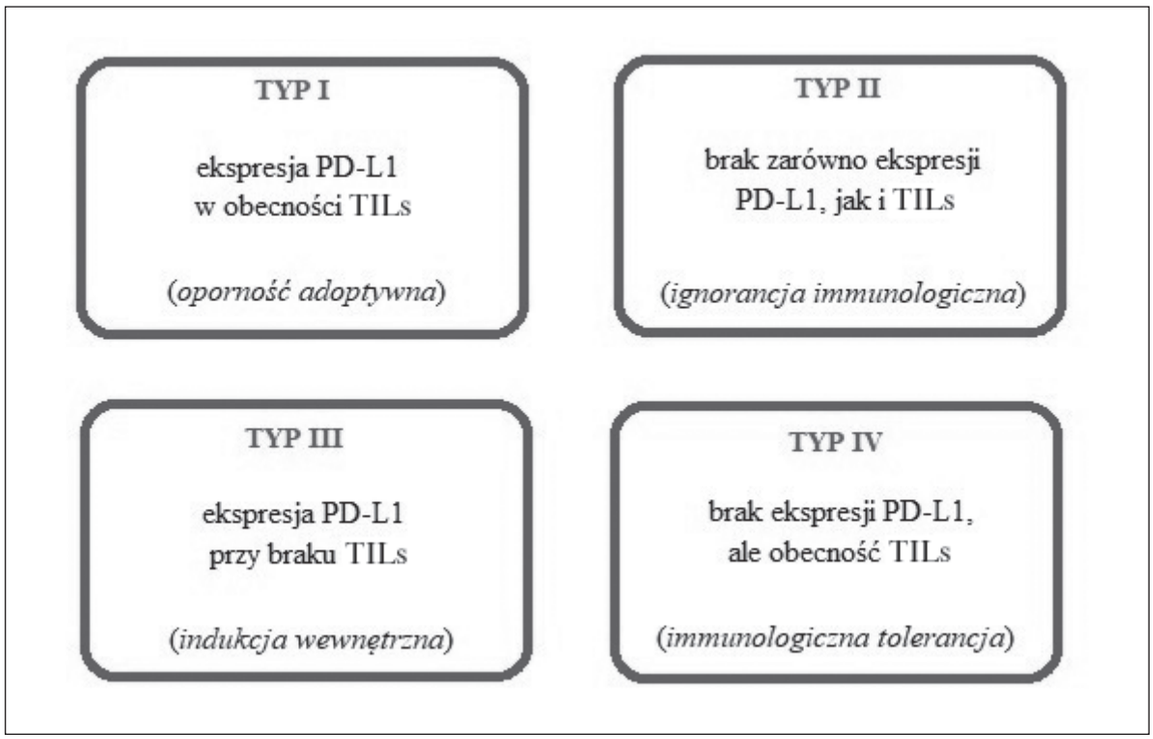
Szlak programowanej śmierci komórki PD-1/PD-L1 (*programmed cell death protein 1/ programmed cell death-ligand 1*) ogrywa kluczową rolę w kontroli interakcji między limfocytami T a innymi komórkami [4]. Receptory transbłonowe PD-1, wykrywane są głównie na aktywowanych limfocytach T i ulegają interakcji z białkiem PD-L1, którego ekspresję wykazano na komórkach nowotworowych oraz prezentujących antygen (APCs – *antigen presenting cells*). Prowadzi to do dezaktywacji limfocytów T i zahamowania odpowiedzi immunologicznej [4, 5]. Nadekspresja ligandu PD-L1 na komórkach nowotworowych prowadzi do upośledzenia funkcji cytotoksycznych limfocytów T [4]. Wykrycie ekspresji PD-L1 na powierzchni komórek OC pozwoliło na zaprojektowanie badań przedklinicznych i klinicznych z zastosowaniem przeciwciał monoklonalnych (mAbs – *monoclonal antibodies*) anty-PD-1 oraz anty-PD-L1. Aktualnie prowadzone badania z ich wykorzystaniem w terapii OC znajdują się na wczesnym etapie zaawansowania (głównie I i II faza badań klinicznych). Badane są zarówno mAbs skierowane przeciwko receptorowi PD-1 tj. niwolumab, pembrolizumab, jak i przeciwko ligandowi PD-L1 tj. awelumab, durwalumab, atezolizumab. Żaden z wymienionych immunoterapeutyków nie jest zatwierdzony przez FDA w terapii raka jajnika. W prowadzonych badaniach odsetek obiektywnych odpowiedzi na leczenie (OR – *overall response*), który jest sumą odpowiedzi całkowitej (ang. *complete remission*) na (CR – *complete remission*) i częściowej (PR – *partial remission*) waha się od 5,9% do 15% [6]. Niezadawalające wyniki kliniczne skłaniają badaczy do poszukiwania bardziej efektywnych terapii, jakimi wydają się być terapie skojarzone, a także do odpowiedzi na pytanie, jakie mechanizmy obronne komórki nowotworowej prowadzą do powstania oporności na stosowane terapie?

U chorych na czerniaka wykazano, że rodzaj odpowiedzi klinicznej indukowanej w efekcie blokady PD-1, jest zależny od obecności limfocytów T infiltrujących i ekspresji PD-L1 w mikrośrodowisku guza. Na tej podstawie wyodrębniono cztery typy oporności u chorych na nowotwór (Ryc. 1) [7].

Szlak PD-1/PD-L1 jest obiecującym celem immunoterapii w nowotworach, a profil ekspresji PD-L1 w odniesieniu do TILs okazuje się być ważną determinantą odpowiedzi klinicznej. Wykazano, iż blokada szlaku PD-1/PD-L1 jest najbardziej skuteczna w przypadku obecności limfocytów $CD8^+$ i ekspresji PD-L1. Taube i wsp. jako pierwsi wykazali, że wydzielany przez limfocyty T IFN-γ stanowi jeden z czynników zwiększających ekspresję PD-L1 na komórkach nowotworowych, dostarczając bezpośredniego dowodu na mechanizm oporności adoptywnej za pośrednictwem IFN-γ [8]. Oceniając poziom ekspresji PD-L1 na komórkach guza i odpowiedź na blokadę PD-1 wykazano, że PD-L1 ulega indukowanej ekspresji najczęściej przy infiltracji limfocytami T i zwiększeniu stężenia IFN-γ. Natomiast kolokalizacja PD-L1, PD-1 i komórek T $CD8^+$ w guzie jest związana z bardziej efektywną odpowiedzią na blokadę PD-1.

PD-L1 może również ulegać konstytutywnej ekspresji na drodze różnych mechanizmów. Dotychczas nie zostało wyjaśnione, czy obecność jedynie PD-L1 przy jednoczesnym braku TILs jest korzystnym, czy też niekorzystnym zjawiskiem w przypadku terapii blokującej PD-1. Biorąc pod uwagę powyższe, w nowotworach, które wykazują silną ekspresję PD-L1, ale nie są nacieczone przez limfocyty T $CD8^+$, nie dojdzie do odpowiedzi na tę terapię. Co interesujące, wyjątkiem jest chłoniak Hodgkina, w którym komórki Reed-Stenberga mają amplikon PDJ warunkujący konstytutywną ekspresję PD-L1. W przypadku tego nowotworu stwierdzono lepsze efekty przeciwnowotworowe monoterapii anty-PD-1 [9].

Webb i wsp. dowiedli, że w raku jajnika receptor PD-1 ulega selektywnej ekspresji na TILs w lokalizacji śródnabłonkowej. Autorzy wykazali, że receptor PD-1 ulega koekspresji z cząsteczką CD103, podjednostką integryny, która ułatwia infiltrację guza przez TILs [10]. W przeprowadzonym badaniu wykazano ekspresję PD-L1 na makrofagach związanych z nowotworem (ang. *tumor-associated*) na (TAMs) i była ona silnie związana z TILs oraz powszechna we wszystkich typach histologicznych raka jajnika. Ponadto, ekspresja PD-L1 była wyższa na TAMs niż na komórkach nowotworowych. Jedynie 13,2% guzów o wysokim stopniu złośliwości (HGSC – *high grade serous*



Ryc. 1. Typy oporności na immunoterapię u osób chorych na nowotwór.

carcinoma,) wykazywało ekspresję PD-L1. Wszystkie z nich były infiltrowane przez makrofagi PD-L1$^+$ [10]. Odkrycia Webb i wsp. definiują TAMs jako główne źródło ekspresji PD-L1 w raku jajnika i demonstrują pozytywną zależność pomiędzy ekspresją PD-L1, TILs i przeżyciem pacjentek w grupie z surowiczym OC o wysokim stopniu złośliwości, u których wykonano maksymalną cytoredukcję. Zatem zgodnie z koncepcją oporności adoptywnej, ekspresja PD-L1 wydaje się być wskaźnikiem prognostycznie korzystnych odpowiedzi TILs w HGSC.

Aust i wsp. wykazali, że niski odsetek komórek raka jajnika wykazuje ekspresję PD-L1. Co ciekawe, była ona zaobserwowana wyłącznie na komórkach nowotworowych z sąsiadującymi TILs [11]. Guzy oceniano jako pozytywne pod względem PD-L1, jeśli ≥1% komórek nowotworowych w obrębie całego obszaru guza wykazywało ekspresję PD-L1. Analizując wyniki, ekspresję PD-L1 wykazano w 75% guzów pierwotnych oraz w 40% próbek z ognisk przerzutowych. Dodatkowo, autorzy wykazali pozytywną zależność pomiędzy ekspresją PD-L1 a całkowitym czasem przeżycia pacjentek z OC. W przytoczonym badaniu, zarówno w pierwotnych jak i w przerzutowych guzach, zaobserwowano znacznie częstsze występowanie limfocytów CD8$^+$ infiltrujących guza w preparatach z komórkami nowotworowymi wykazującymi ekspresję PD-L1. Ekspresja PD-L1 dodatnio korelowała z limfocytami T CD8$^+$, limfocytami B oraz odsetkiem Tregs we krwi obwodowej. Co ciekawe, konstytutywny i znaczny wzrost ekspresji PD-L1 obserwowano w drugiej wznowie w porównaniu z pierwszym nawrotem i pierwotnymi guzami surowiczymi [11].

CZYNNIKI INDUKUJĄCE EKSPRESJĘ PD-L1

Ekspresja PD-L1 może być indukowana przez cytokiny, takie jak IL-2, IL-7, IL-15, IL-10 i IL-32γ [8]. Poza cytokinami, również hipoksja może indukować ekspresję PD-L1 poprzez szlak czynnika HIF-1α (*hypoxia-inducible factor 1α*) [12]. Regulacja ekspresji PD-L1 może również różnić się w zależności od typu komórki. Wykazano, że IL-10 i IL-32γ mogą indukować ekspresję PD-L1 na komórkach szpikowych, ale nie na komórkach nowotworowych [12].

Cechą charakterystyczną większości guzów litych jest ich nieprawidłowe unaczynienie. Ułatwia ono ucieczkę nowotworu spod nadzoru immunologicznego, upośledza perfuzję i przedostawanie się leków z krążenia, ograniczając ich działanie przeciwnowotworowe. Nieprawidłowości naczyniowe wynikają z podwyższonych poziomów czynników proangiogennych, takich jak czynnik wzrostu śródbłonka naczyń (VEGF – *vascular endothelial growth factor*) i angiopoetyna 2 (ANG2). Leki skierowane przeciwko tym cząsteczkom mogą poprawić odpowiedź na terapie. Częściowo jest to spowodowane poprzez normalizację nieprawidłowego unaczynienia, co nasila infiltrację guza przez efektorowe komórki odpornościowe i może przekształcić samoistnie immunosupresyjne mikrośrodowisko guza (TME – *tumor microenvironment*) w immunokompetentne. Zmienione mikrośrodowisko może modulować aktywność i skuteczność leków oraz komórek układu immunologicznego w guzie [13].

VEGF wykazuje różne aktywności w TME, a jego podwyższone stężenie indukuje immunosupresję związaną z nowotworem za pośrednictwem czterech różnych mechanizmów. Po pierwsze, podwyższony poziom VEGF

bezpośrednio hamuje migrację, proliferację i funkcję efektorową limfocytów Tc. Po drugie, VEGF hamuje dojrzewanie komórek dendrytycznych (DCs – *dendritic cells*) i prezentację antygenu, co tłumi aktywację limfocytów T, hamując odpowiedź immunologiczną. Po trzecie, wysokie stężenie VEGF sprzyja rekrutacji i proliferacji komórek immunosupresyjnych, w tym komórek Tregs, MDSCs i pronowotworowych TAMs. Wreszcie, VEGF promuje angiogenezę, która powoduje nieprawidłowe unaczynienie guza, prowadząc do hipoksji i obniżenia pH w mikrośrodowisku, co sprzyja immunosupresji lokalnej i układowej [13].

ANG2 jest kolejnym kluczowym regulatorem angiogenezy. Jej rola immunomodulująca nie została dobrze poznana. U pacjentek z rakiem jajnika obniżenie stężenia ANG2 w odpowiedzi na hamowanie szlaku VEGF za pomocą sunitynibu koreluje z wydłużeniem czasu przeżycia wolnego od progresji choroby [14]. Wykazano, że ekspresja ANG2 w guzie lub jej stężenie w surowicy krwi korelują z krótszym przeżyciem chorych w różnych typach nowotworów, w tym w raku jajnika. ANG2 może zatem okazać się potencjalnym czynnikiem predykcyjnym i/lub prognostycznym [15].

WYBRANE MECHANIZMY OPORNOŚCI NA LECZENIE ANTYANGIOGENNE

Nowotwory mogą rozwijać oporność na terapię anty-VEGF. Jednym z kluczowych mediatorów tego zjawiska jest hipoksja wywołana ekspozycją na te leki [16]. Wyróżnia się szereg mechanizmów oporności na leczenie antyangiogenne. Należy do nich aktywacja alternatywnych szlaków angiogenezy (takich jak sygnalizacja ANG2/TIE2), zwiększenie inwazyjnego charakteru komórek nowotworowych, rekrutacja proangiogennych komórek szpikowych, zwiększona ilość perycytów w naczyniach krwionośnych guza oraz alternatywne sposoby rekrutacji naczyń (koopcje naczyń) [16]. W badaniach Schmittnaegel i wsp., podwójna terapia antyangiogenna z przeciwciałem anty-VEGF-ANG2 doprowadziła do wzrostu ekspresji PD-L1 na komórkach śródbłonka i komórkach nowotworowych w wielu modelach nowotworów myszy, powodując zahamowanie odpowiedzi przeciwnowotworowej. Jednak równoczesne leczenie przeciwciałem anty-PD-1 pozwala na utrzymanie kontroli nad chorobą nowotworową [17].

Ukierunkowanie terapii zarówno na szlak VEGF, jak i ANG2 jednocześnie, zwiększa skuteczność terapii antyangiogennych. Podwójna blokada VEGF-ANG2 przedłuża okres przeżycia w porównaniu z monoterapią anty-VEGF lub anty-ANG2 w mysich modelach glejaka [18], czerniaka, guzów neuroendokrynnych trzustki i przerzutów lub wczesnych etapów raka piersi, czego nie obserwuje się w raku nerki [13]. Wykazano również, że podwójne hamowanie VEGF-ANG2 jest bardziej skuteczne niż monoterapia anty-VEGF w modelach raka sutka. Świadczy o tym zmniejszone powstawanie przerzutów i mikroprzerzutów [19]. Z kolei w III fazie badania klinicznego TRINOVA-1, w którym kobiety z nawrotem raka jajnika były leczone trebananibem i paklitakselem, tylko pacjentki z wodobrzuszem uzyskały istotną statystycznie poprawę ogólnego czasu przeżycia [20].

Podsumowując, odkrycia te sugerują, że korzyść z podwójnej terapii przeciwangiogennej zależy od typu nowotworu, stopnia progresji choroby, specyficznych cech TME, obecności płynu otrzewnowego, a także dawki i czasu podawania leku. Obecnie prowadzone są próby kliniczne, oceniające podwójne hamowanie VEGF i ANG2 u pacjentów z nowotworami.

Inhibitory punktów kontrolnych i leki antyangiogenne są coraz częściej wykorzystywane i nadal testowane w badaniach klinicznych. Terapia ICB (*immune checkpoint blockade*) może znacznie wydłużyć czas przeżycia określonej grupy pacjentek, które wykazują trwałą odpowiedź, ale nie poprawia wyników większości chorych. Leki antyangiogenne nieznacznie wydłużają czas przeżycia (od kilku tygodni do kilku miesięcy), przy rzadkich trwałych odpowiedziach. Dostrzegalny jest potencjał terapii kombinowanych, które wydłużają czas przeżycia w porównaniu z monoterapią. Wyniki badań klinicznych wskazują, że potencjalna korzyść z takich terapii wynika z modulacji zarówno układu naczyniowego guza, jak i mikrośrodowiska, w którym nowotwór się rozwija [13]. Immunoterapia opiera się na akumulacji i zwiększeniu aktywności komórek efektorowych układu odpornościowego w TME. W związku z tym łączenie antyangiogennych terapii i terapii celowanych może zwiększyć skuteczność immunoterapii i zmniejszyć ryzyko skutków ubocznych, w szczególności związanych z odpornością, takich jak autoimmunologiczne zapalenie jelita grubego [13].

Makrofagi związane z guzem również wydają się modulować odpowiedź na immunoterapię. Wśród TAMs wyróżnia się makrofagi M1, które są zaangażowane w promowanie odporności przeciwnowotworowej, jak i makrofagi M2, które wykazują właściwości pronowotworowe [21]. Wykazano, że przeprogramowanie pronowotworowych makrofagów M2 w kierunku fenotypu M1 o działaniu przeciwnowotworowym, w dużym stopniu przyczynia się do skuteczności terapeutycznej podwójnej terapii antyangiogennej skierowanej przeciwko VEGF i ANG2 [17, 18]. W celu przezwyciężenia potencjalnego mechanizmu oporności makrofagów, badacze przetestowali blokadę receptora czynnika wzrostu stymulującego kolonie makrofagów (CSF-1R), w mysim modelu raka trzustki. Wykazano zmniejszoną ilość TAM, z późniejszym wzrostem wytwarzania interferonu i ograniczoną progresją guza. Co istotne, blokada PD-1 czy też CTLA-4 nie ograniczały znacząco wzrostu nowotworu w modelu mysim [22]. Jednak blokada CSF-1R w połączeniu z przeciwciałem przeciwko PD-1 lub CTLA-4, (poza gemcytabiną), doprowadziła do częściowej regresji guza [22]. Dane te sugerują, że blokada wywołana przez CSF-1R powodowała redukcję TAMs, co umożliwiło odpowiedź na terapię immunologiczną. W przedklinicznych modelach glejaka niedobór makrofagów i mAbs skierowane przeciwko czynnikowi znosiły korzyści z podwójnego hamowania VEGF-ANG2, potwierdzając tym samym rolę TAMs w pośredniczeniu w efektach leczenia [18].

Rozważając mechanizmy oporności nowotworów należy wspomnieć o oporności adoptywnej. Polega ona na produkcji IFN-γ przez aktywowane limfocyty T infiltrujące guza. Indukuje to ekspresję PD-L1 na komórkach nowotworowych i komórkach układu immunologicznego. Połączenie ligandu PD-L1 z receptorem PD-1 przekazuje sygnał śmierci na wczesnym etapie rozwoju. Komórki, które wykazują zwiększoną ekspresję PD-L1 hamują aktywację limfocytów T, co prowadzi do supresji odpowiedzi przeciwnowotworowej. IFN-γ indukuje skuteczną przeciwnowotworową odpowiedź immunologiczną poprzez zwiększenie ekspresji cząsteczek MHC, stymulację migracji komórek układu immunologicznego oraz bezpośrednią aktywność antyproliferacyjną i proapoptotyczną w stosunku do komórek nowotworowych [23]. Jednak ciągła ekspozycja na IFN-γ może indukować ekspresję PD-L1 i prowadzić do ucieczki komórek nowotworowych spod nadzoru immunologicznego [24].

Układ immunologiczny różnicuje komórki nowotworowe i prawidłowe. Najczęstszy mechanizm tego rozpoznawania jest związany ze zwiększonym ładunkiem mutacyjnym w nowotworach [9]. Mutacje, które pojawiają się w komórce nowotworowej gospodarza i są przenoszone przez większość komórek potomstwa (mutacje klonalne) są bardziej korzystne niż mutacje, które pojawiają się później, w trakcie choroby (mutacje subklonalne). Mutacje subklonalne mogą się różnić w zależności od rodzaju komórek nowotworowych, co powoduje, że leczenie mAbs opartymi na szlaku PD-1/PD-L1 nie jest skuteczne [25].

Najczęstszym powodem, dla którego nowotwór nie ma poprzedzającej infiltracji limfocytami T, jest prawdopodobnie stan niskiej immunogenności wynikający z braku mutacji, które stały się rozpoznawalnymi neoantygenami lub aktywnym środkiem wykluczającym limfocyty T [24]. Niektóre fenotypy nowotworowe mogą przyczyniać się do braku rozpoznawania limfocytów T, np. ekspresja genów szlaku Wnt lub IPRES (wrodzona oporność anty-PD-1/pierwotna oporność na immunoterapię) [9]. Jest również możliwe, że limfocyty T wykazujące aktywność przeciwnowotworową są upośledzone przez punkt kontrolny (np. CTLA-4) lub komórki o właściwościach supresyjnych (MDSCs lub Tregs) mikrośrodowiska guza [24]. Ekspresja hamujących receptorów punktów kontrolnych, takich jak CTLA-4, PD-1, LAG3, TIM3, TIGIT przez komórki T jest mechanizmem, dzięki któremu guzy unikają lub tłumią odporność gospodarza przez negatywną regulację funkcji komórek T. Blokada receptorów za pomocą swoistych przeciwciał ma na celu przywrócenie istniejącej odpowiedzi przeciwnowotworowej. Obecnie trwają badania kliniczne nad wpływem przeciwciał, skierowanych przeciwko PD-1, PD-L1 oraz CTLA-4 u pacjentek z OC. Połączenie terapii anty-CTLA-4 oraz anty-PD-1 i PD-L1 zostało zatwierdzone jako leczenie pierwszego rzutu u pacjentów z zaawansowanym czerniakiem i jest testowane w innych typach nowotworów, z wykorzystaniem różnych dawek i odstępów czasu między anty-CTLA-4 w celu zmniejszenia toksyczności [24]. Mimo, iż terapia mAbs ma wpływ na regresję czerniaka i innych guzów litych, w raku jajnika wskaźniki odpowiedzi były niskie.

Główną przeszkodą w pomyślnym wdrożeniu immunoterapii u pacjentek z rakiem jajnika jest immunosupresyjne mikrośrodowisko guza. Liczne badania ukazały niektóre dominujące mechanizmy oporności immunologicznej w raku jajnika włączając zewnętrzną supresję komórek efektorowych $CD8^+$ przez Tregs, MDSCs [2], deregulację metaboliczną poprzez katabolizm tryptofanu przez 2,3-dioksygenazę indoleaminy (IDO), związanie hamującego receptora PD-1 z ligandem PD-L1 i czynniki hamujące, takie jak TGF-β. Mechanizmy te ułatwiają progresję nowotworu poprzez aktywne hamowanie endogennej odporności przeciwnowotworowej i stanowią ważną przeszkodę, którą należy przezwyciężyć w celu wdrożenia skutecznej immunoterapii [1].

W immunogennym guzie, aby wywołać swoistą odpowiedź limfocytów T, komórki nowotworowe mogą podlegać wielu procesom genetycznym i niegenetycznym, aby uniknąć eliminacji przez układ odpornościowy, określanej jako immunoedycja nowotworowa [9]. Może ona skutkować utratą mutacji najbardziej immunogennych lub mutacją czy też zmniejszoną ekspresją genów zaangażowanych w szlak prezentacji antygenów. Każde z tych zdarzeń może wywołać pierwotną lub nabytą oporność na blokadę PD-1. Silny wpływ mechanizmów immunologicznych może prowadzić do kształtowania mutacyjnego profilu nowotworu, specyficznej delecji ludzkiego antygenu leukocytarnego (HLA) klasy I lub do utraty β-2-mikroglobuliny (B2M). B2M jest niezbędna do syntezy i transportu HLA klasy I na powierzchnię komórki, a jej wrodzony niedobór prowadzi do zaburzeń w rozpoznawaniu Ag przez limfocyty $CD8^+$ [9].

Co ciekawe, wykazano różnice w efektywności leczenia nowotworów, które są nacieczone limfocytami T (tzw. guzów gorących) i zimnych guzów, pozbawionych TILs. Podczas gdy w przypadku guzów gorących skuteczna może być monoterapia, guzy zimne wymagają użycia kombinacji leków, ponieważ nie są rozpoznawane przez komórki układu immunologicznego. Naukowcy zmierzają do transformacji immunologicznie „zimnych" guzów w „gorące".

Obecnie trwają prace mające na celu opracowanie skutecznych strategii zwalczania oporności na immunoterapię. Leczenie za pomocą molekularnie ukierunkowanej terapii może pomóc w przekształceniu mikrośrodowiska, czego dowodem jest zwiększona ekspresja PD-L1 poprzez zjawisko oporności adoptywnej [8, 26].

Należy pamiętać, że odpowiedź immunologiczna jest dynamiczna i stale ewaluuje u każdego pacjenta, albo w wyniku czynników środowiskowych i genetycznych pacjenta, albo w wyniku interwencji terapeutycznych, w tym chirurgii, chemioterapii, radioterapii i immunoterapii. Zapewnienie korzyści klinicznej dla pacjentów wymaga pełnego zrozumienia mechanizmów, które doprowadziłyby do skutecznej odpowiedzi przeciwnowotworowej, a także różnych czynników wewnętrznych związanych z nowotworem i czynników specyficznych, które skutkują pierwotną, adoptywną i nabytą opornością na immunoterapię. Wyjaśnienie tych mechanizmów ujawni ważne wskazówki dotyczące kolejnych kroków, które należy podjąć, aby potencjalnie znieść oporność na immunoterapię.

PIŚMIENNICTWO

1. Odunsi K. Immunotherapy in ovarian cancer. Ann Oncol. 2017;28:vii1-7.
2. Sato E, Olson SH, Ahn J et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci U S A. 2005;102(51):18538-18543.
3. Hwang WT, Adams SF, Tahirovic E, Hagemann IS, Coukos G. Prognostic significance of tumor-infiltrating T cells in ovarian cancer: a meta-analysis. Gynecol Oncol. 2012;124(2):192-198.
4. Pietzner K, Nasser S, Alavi S et al. Checkpoint-inhibition in ovarian cancer: rising star or just a dream? J Gynecol Oncol. 2018;29(6):e93. doi: https://doi.org/10.3802/jgo.2018.29.e93.
5. Piętak P, Pietrzyk N, Pawłowska A et al. The meaning of PD-1/PD-L1 pathway in ovarian cancer pathogenesis. Wiad Lek. 2018;71(5):1089-1094.
6. Gadducci A, Guerrieri ME. Immune Checkpoint Inhibitors in Gynecological Cancers: Update of Literature and Perspectives of Clinical Research. Anticancer Res. 2017;37(11):5955-5965.
7. Teng MW, Ngiow SF, Ribas A, Smyth MJ. Classifying cancers based on T-cell infiltration and PD-L1. Cancer Res. 2015;75(11); 2139-2145.
8. Taube JM, Anders RA, Young GD et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med. 2012;4(127):127ra37. doi: 10.1126/scitranslmed.3003689.
9. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-1355.
10. Webb JR, Milne K, Kroeger DR, Nelson BH. PD-L1 expression is associated with tumor-infiltrating T cells and favorable prognosis in high-grade serous ovarian cancer. Gynecol Oncol. 2016;141(2):293-302.
11. Aust S, Felix S, Auer K et al. Absence of PD-L1 on tumor cells is associated with reduced MHC I expression and PD-L1 expression increases in recurrent serous ovarian cancer. Sci Rep. 2017; 7:42929. doi: 10.1038/srep42929.
12. Noman MZ, Desantis G, Janji B et al. PD-L1 is a novel direct target of HIF-1alpha, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. J Exp Med. 2014;211:781–790.
13. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol. 2018;15(5):325-340.
14. Bauerschlag DO, Hilpert F, Meier W et al. Evaluation of potentially predictive markers for anti-angiogenic therapy with sunitinib in recurrent ovarian cancer patients. Transl Oncol. 2013;6:305–310.
15. Sallinen H, Heikura T, Laidinen S et al. Preoperative angiopoietin-2 serum levels: a marker of malignant potential in ovarian neoplasms and poor prognosis in epithelial ovarian cancer. Int J Gynecol Cancer. 2010;20:1498–1505.
16. Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. Cancer Cell. 2014;26:605–622.
17. Schmittnaegel M, Rigamonti N, Kadioglu E et al. Dual angiopoietin-2 and VEGFA inhibition elicits antitumor immunity that is enhanced by PD-1 checkpoint blockade. Sci Transl Med. 2017;9:eaak9670. doi: 10.1126/scitranslmed.aak9670.
18. Peterson TE, Kirkpatrick ND, Huang Y et al. Dual inhibition of Ang-2 and VEGF receptors normalizes tumor vasculature and prolongs survival in glioblastoma by altering macrophages. Proc Natl Acad Sci USA. 2016;113:4470–4475.
19. Kienast Y, Klein C, Scheuer W et al. Ang-2–VEGF-A CrossMab, a novel bispecific human IgG1 antibody blocking VEGF-A and Ang-2 functions simultaneously, mediates potent antitumor, antiangiogenic, and antimetastatic efficacy. Clin Cancer Res. 2013;19:6730–6740.
20. Monk BJ, Poveda A, Vergote I et al. Final results of a phase 3 study of trebananib plus weekly paclitaxel in recurrent ovarian cancer (TRINOVA-1): long-term survival, impact of ascites, and progression-free survival-2. Gynecol Oncol. 2016;143:27-34.
21. Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers. 2014;6:1670–1690.
22. Zhu Y, Knolhoff BL, Meyer MA et al. CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. Cancer research. 2014;74:5057–5069.
23. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. Nat Rev Immunol. 2005;5:375–386.
24. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017;168(4):707-723.
25. McGranahan N, Furness AJ, Rosenthal R et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science. 2016;351(6280):1463-1469.
26. Pawłowska A, Suszczyk D, Okła K, Barczyński B, Kotarski J, Wertel I. Immunotherapies based on PD-1/PD-L1 pathway inhibitors in ovarian cancer treatment. Clin Exp Immunol. 2019;195(3):334-344.

Konflikt interesów:
Wszyscy autorzy deklarują brak konfliktu interesów.

AUTOR KORESPONDUJĄCY
Iwona Wertel
Pracownia Immunologii Nowotworów
I Katedry i Kliniki Ginekologii Onkologicznej i Ginekologii
Uniwersytetu Medycznego w Lublinie
ul. Staszica 16, 20-081, Lublin
e-mail: iwonawertel@wp.pl

Nadesłano: 18.04.2019
Zaakceptowano: 20.05.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

PERSPECTIVE FOR EVALUATION OF MICRORNA IN PLASMA AND BILE FOR DIFFERENTIAL DIAGNOSIS OF OBSTRUCTIVE BILIARY TRACT DISEASE

Oleg M. Terletskiy, Vasyl I. Kolomiytsev, Oleksiy V. Lukavetskiy, Mariya M. Bufan
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Introduction: Cholelithiasisis diagnosed in 10-25% of the adult population. The manifestation of cholelithiasis in the form of acute cholecystitis, cholangitis, jaundice etc. occurs with a probability of 2-3% or more per year depending on the risk factors. Most often, it manifests it self as acute calculous cholecystitis. Up to 20% of such patients have additional calculi in extrahepatic bile ducts requiring simultaneous surgical intervention. Currently, the algorithm for diagnosis of concomitant choledocholithiasis in acute cholecystitis is multilevel and it needs to be simplified and improved. Conventional non-invasive diagnostic techniques have low specificity and sensitivity. A new safe diagnostic test is needed for the diagnosis of choledocholithiasis in cholecystitis in order to improve the results of surgical treatment of patients.

The aim of the study **-** to determine the prospects for diagnosis of microRNA for differential diagnosis of obstructive diseases of the biliary tract on the basis of the literature data.

Materials and methods: The analysis of the selected international literature in the period of 1991-2018 concerning the studies of microRNA in cholestatic liver diseases was carried out. The search for literature was conducted using Google Scholar and PubMed search engines for the following keywords: microRNA, cholestasis, choledocholithiasis, acute cholecystitis, biliary obstruction in their various combinations.

Review: MicroRNA is a specific post-transcriptional regulator of gene expression in all organs and systems of the body. There are specific types of miRNAs for different tissues. The most studied type of liver miRNA is miR-122. The studies showed better sensitivity and specificity of the detection of miR-122 both in the plasma and in the bile for the diagnosis of pathological liver conditions compared with conventional liver tests (aminotransferase, alkaline phosphatase, gamma-glutamyltransferase). Regarding the cholestatic hepatocyte injury occurring in choledocholithiasis, the following types of miRNA were identified: 122, 21, 29, 125, 222, let-7, 98 etc. Their concentrations in plasma and bile can be used as a diagnostic test for the presence of concomitant benign cholestasis in acute cholecystitis. Moreover, these markers can be used for the differential diagnosis of cholestasis of different etiology.

Conclusions: Quantitative and qualitative characteristics of microRNA in bile and plasma can be used as an additional non-invasive method for diagnosis of cholestasis induced by choledocholithiasis in acute calculous cholecystitis. Further studyis needed to identify the most optimal algorithm for the administration of microRNA in clinical practice.

KEY WORDS: microRNA, cholestasis, diagnosis, choledocholithiasis, acute cholecystitis, biliary tract obstruction

Wiad Lek 2019, 72, 7, 1403-1407

INTRODUCTION

Cholelithiasisis the most common cause of non-malignant hepatobiliary diseases in the general population [1]. About 10-15% of males and 20-25% of females have stones in the biliary tract. Up to 20% of patients with calculous cholecystitis simultaneously have calculi in the choledoch or common bile duct. About 50% of patients with cholelithiasis do not notice any specific symptoms of the disease and can complain only of general weakness and fatigue [1]. The symptoms of the obstructive hepatobiliary disease such as colic, jaundice, etc. [2, 3] develop in 2-4% of patients with gallstones within one year.

Most often, cholelithiasis manifests as acute cholecystitis, which according to modern guidelines requires surgical intervention in the form of cholecystectomy [3]. It is essential that stones are also found in the common bile duct or choledoch in about 20% of patients during the laparoscopic cholecystectomy [4]. In the surgical treatment of acute cholecystitis, the simultaneous removal of calculi from extrahepatic bile ducts, if they are present, can improve the results of the operation and prevent the development of such complications as acute cholangitis and acute pancreatitis in the future. Therefore, the pressing issue is the precise diagnosis of concomitant choledocholithiasis in acute cholecystitis in order to reduce the risk of postoperative complications and decrease overall economic costs for the patient [3].

The conventional diagnostic algorithm consists of a survey and inspection, laboratory tests and instrumental diagnostic techniques (ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiopancreatography). However, ultrasound and tests of such liver markers as aminotransferases, alkaline phosphatase, bilirubin, and gamma-glutamyltransferase are not sufficiently sensitive and specific methods [5, 6]. The use of invasive diagnostic techniques is associated with the risk of complications and they are expensive. Thus, the topical issue is the introduction to the clinical practice of a specific and sensitive marker for the diagnosis of choledocholithiasis in both asymptomatic patients and those who are referred to undergo cholecystectomy.

THE AIM

The aim of the study - to determine the prospects for diagnosis of microRNA for differential diagnosis of obstructive diseases of the biliary tract on the basis of the literature data.

MATERIALS AND METODS

The analysis of the selected international literature in the period of 1991-2018 concerning the studies of microRNA in cholestatic liver diseases was carried out. The search for literature was conducted using Google Scholar and PubMed search engines for the following keywords: cholestasis, choledocholithiasis, microRNA, acute cholecystitis, biliary obstruction in their various combinations.

REVIEW AND DISCUSSION

MICRORNA

MicroRNA (miRNA, miR) is a group of physiologically active non-coding endogenous RNAs of 19-23 nucleotides in length, the main role of which is the post-transcriptional regulation of the expression of certain genes [6, 7]. The mechanism for regulating expression is to bind complementary nucleotide sequences to the matrix RNA blocking the translation in the ribosomes. However, miRNAs can also interact with repressor proteins by blocking them, which, on the contrary, activates the expression of target genes [6, 7]. To date, more than a 1,000 different types of miRNAs have been identified, which can be either organ- and tissue-specific, or universal.

The microRNA in biological fluids can be found in specific transfer vesicles called extracellular vesicles, which, along with the microRNA, transfer other biologically active substances, or it can be bound to transport proteins [8]. On the other hand, thereis also cell-free circulating microRNA that has high stability in almost all biological fluids [5, 9, 10]. Currently, methods for precise identification of miRNA in different types of biological fluid (plasma, saliva, bile, etc.) are available with the help of PCR [6]. Concerning liver diseases, the most reasonable is the evaluation of miRNA in plasma and bile collected during gastroduodenoscopy or ERCP.

As a result of pathological processes in cells, the structure of both intercellular and intracellular miRNAs varies considerably [5, 7, 8, 10, 11]. Thus, depending on the etiology of liver damage, the concentrations of various types of miRNA may change, which has high levels of specificity and sensitivity to certain diseases [4, 5, 10, 12, 13, 14, 15]. Concerning liver diseases, the miRNA has the largest evidence base to diagnose and predict the success of therapy in oncological processes [5, 7]. However, the study of miRNAs in acute and chronic cholestatic liver diseases is promising.

MICRORNA AS A MARKER FOR HEPATOCYTE INJURY

Cholangiocytes are cells forming the walls of the biliary tree of the liver and the external biliary tract, account for 3-5% of the total number of hepatocytes, but they, in turn, synthesize up to 40% of the daily amount of bile [5, 7, 16]. If the hepatobiliary system is obstructed due to the presence of stones in the extrahepatic biliary tract, cholangiocytes first experience morphological signs of oxidative stress due to the direct toxic effects of bile [5]. As an adaptive reaction, certain types of miR may alter their synthesis activity to activate intracellular antioxidant and regulatory systems [5]. The role of miRNA as a regulator of adaptive gene expression was confirmed on the model of experimental atresia of extrahepatic bile ducts in the integrative study of Bessho K. et al. [17]. Such regulation provides an adequate proliferative response to cholestatic injury enabling to maintain the normal morphology of the hepatobiliary tree during short-term cholestasis [16, 17]. Unfortunately, the adaptive capacity of cholangiocytes is lost in long-term cholestasis and fibrosis may progress. Thus, changes in the concentration of miRNAs can be considered as the process of cell adaptation to certain homeostatic conditions, not just as a marker of cytotoxic damage. Determining the changes in the structure and concentration of certain miRNAs can be a powerful diagnostic test for a significant number of liver and biliary tract diseases.

YamauraY. et al. in their study showed that a different pathophysiological reaction occurs in cholangiocytes depending on the etiology of cholestasis (toxic or mechanical), which is accompanied by the change in the concentration of various profiles of plasma miRNA [6]. Two models of cholestatic liver damage were used in mouse study: introducing a-naphthyl isothiocyanate (ANIT) and applying a ligature to the bile duct. Further, changes in the profiles of plasma miRNA were recorded. As a result, changes in the concentration of different types of miRNAs were found depending on the type of cholestatic damage, indicating a high specificity of the marker [6]. Such results confirm the potential of the miRNA as a marker for the differential diagnosis of diseases of the hepatobiliary tree.

Thirteen different types of miRNA were identified in the study by Schaap F. G. et al.,which were significantly associated with extrahepatic cholestasis [18]. It is of interest to note that the concentration of some types of miRNAs may increase, and of others, on the contrary, decrease [18, 19]. However, the most studied type of liver miRNA is miR-122, which accounts approximately for 70% of all liver miRNAs [5, 6, 15]. This type of miRNA plays an important role in the synthesis of cholesterol by hepatocytes [9, 15]. A hyperexpression of a large number of liver genes occurs and hepatocytes decrease the production of cholesterol when this type of miRNA is blocked [15]. It is also important to note that secretion of both bilirubin and miR-122 into bile are interrelated processes [20]. Thus, in the study by Verhoeven C. J. et al., mutual positive correlation between the levels of bilirubin and miR-122 in bile was established at different pathological states of the liver [20].

There are data suggesting a significantly higher sensitivity and specificity of miR-122 for the diagnosis of hepatocyte injury due to primary sclerosis of the biliary tract, sclerosing cholangitis, polycystic liver, extrahepatic obstruction,

etc. compared with conventional biochemical markers of liver [5, 6, 10, 21, 22]. Moreover, changes in the concentration of specific miRNAs occur much faster compared to aminotransferase [10, 22]. Thus, due to the toxicinjury of hepatocytes, the increase in plasma aminotransferase concentration began twelve hours after the toxin injection, and changes in the concentration of miRNAs were recordedthree hours after the study began [10].

Woolbright B. et al. found in the study that plasma levels of miR-122 increased significantly within 48 hours after the ligation of the bile duct [11]. In another study of the toxic injury of cholangiocytes, the concentration of miR-122 increased significantly in the period from 6 to 24 hours [14]. The data are confirmed by other studies by Th'ng F. et al. and Shifeng H. et al. in patients with cholelithiasis [9, 12, 23]. An increase in the concentration of miR-122 in the study group of patients with cholelithiasis was shown, regardless of the presence of symptoms as compared with the controls in both studies [12, 23]. The sensitivity of the diagnostic technique for cholelithiasis by determining the level of miR-122 in plasma reached 77.4%, and the specificity was 96.4% [12]. Moreover, the study by Th'ng F. et al. showed that choledocholithiasis can be differentiated from cholecystitis using miRNA [9]. Thus, patients with choledocholithiasis had statistically more significant increase of miR concentration in plasma compared to patients with cholecystitis [9]. This is primarily due to the degree of obstruction of the hepatobiliary tree, which is usually more pronounced in choledocholithiasis compared with cholecystitis. The miR concentrations were positively correlated with the severity of the inflammatory process in the liver [9].

It is of interest to note thatit is potentially possible to determine the type of pathophysiologic liver damage by determining the concentrations of different types of miRNAs. Thus, chronic injury of hepatocytes (but not cholangiocytes) with fibrosis may lead to the increase in the concentration of miR-122 in plasma, while the concentration of miR-122 in bile may decrease. On the other hand, miR-122 is excreted in both blood and bile in an increased amount in the presence of acute cytotoxic process in the liver. If independently the cholangiocyte is initially damaged, the miR-122 levels may slightly vary, unlike miR-222, the concentration of which increases in plasma and decreases in bile [20].

A specific marker for cholangiocytes is microRNA-222 [20]. Thus, its expression is 17 times more intense in cholangiocytes compared with stromal hepatocytes of a healthy liver. Cholangiocytes are primarily injured in choledocholithiasis, which leads to a disturbance of the barrier function of the outer membrane and the release of miR-222 in both bile and blood [20].

MicroRNA-21 also plays an important role in the pathogenesis of cholestatic liver injury [18]. In the study by Kennedy L. L. et al.,the experimental ligation of the common bile duct led to the increased miR-21 concentration in bile [24]. Taking into account pathophysiological processes, miR-21 stimulates the proliferation of cholangiocytes and their fibrotic transformation [16]. Moreover, inhibition of miR-21 in mice was associated with a decline in local concentrations of proinflammatory factors in the liver and a decrease in the severity of cholestatic fibrosis one week after ligation [24]. Kishimoto T. et al. showed the possibility to distinguish between healthy patients, ones with benign biliary diseases and those with malignant liver neoplasms with the help of miR-21 [25]. Presumably, miR-21 plays a significant role in the proliferation of cholangiocytes, which is significantly more intense in malignant processes than cholestasis. MicroRNA-7-a-1 has antagonist properties with type 21, and vice versa, its level decreases in bile with cholestatic liver injury [16].

MicroRNA-98 and let-7 have suppressive properties for the expression of a large number of proinflammatory liver cytokines [16]. In the study by Glaser S. et al. on the model of cholestatic liver injury in mice, it was found that cholestatic inflammation of cholangiocytes activates the synthesis of the neuroendocrine hormone secretin, which in turn reduces the levels of let-7 and 125b [19]. The result is an increase in the expression of a large number of cytokines, mainly nerve growth factor and vascular endothelial growth factor, which, together with hypersecretion of miR-21, stimulate proliferative degeneration of hepatocytes [16, 19, 25]. MiR-143 and miR-218 have similar properties, which are activated due to cholestatic hepatocyte injury [10].

Bessho K. et al. conducted a study assessing the response of cholangiocytes in extrahepatic bile ducts to experimental cholestasis [17]. As a result, increased expression of miR-29b in cholangiocytes was recorded [17]. Interestingly, intrahepatic hepatocytes respond to cholestasis by activating not the expression of 29b subtype, but of miR-29a [13, 26]. In this regard, further study of the 29b subtype as a specific marker of injury of extrahepatic bile ducts is necessary, which may have a special diagnostic value in choledocholithiasis, regardless of concomitant conditions.

However, it is important not only to define the profile of the miRNA but also to specify the reference limits for different types of disease. Thus, it has been shown that types 517a, 892a and 106a of miRNA may be elevated in both choledocholithiasis and ischemic injury of hepatocytes (liver transplantation) [22, 25]. It is of interest that the increase in concentrations is more significant in ischemic injury [22, 27]. Malignant cholestatic neoplasms of the liver are also accompanied by a more significant change in the miRNA concentrations in both bile and plasma compared with benign cholestasis [5, 10]. These data are the basis for the differential diagnosis of the etiology of obstruction, in the case of ambiguous results of conventional approaches.

There are methods for quantifying the miRNAs without their qualitative evaluation for the diagnosis of certain states. Thus, in the study by Severino V. et al. a quantitative analysis of extracellular vesicles (which is the type of transport for miRNA and other biologically active compounds) in plasma and bile was performed in malignant and benign cholestasis [28, 29]. The result was an increase in the concentrations of extracellular vesicles in both plasma and bile in each type

of cholestasis. It should be noted that the quantitative index allowed differentiating between benign and malignant cholestasis regardless of qualitative evaluation. Quantitative analysis is much more accessible for daily clinical use and does not require significant economic costs [29]. Moreover, it was determined that the analysis of bile and not plasma was significantly more specific (100% for bile versus 63% for plasma) for the diagnosis of cholestasis [29]. This is explained by the inflammatory process largely in cholangiocyte and not in hepatocyte, which makes bile the most sensitive acceptor of cell degradation markers [8]. The data are confirmed by another study, which states that the concentration of specific hepatic miRNAs can be 20 times higher in bile than in plasma [20]. Thus, quantitative and qualitative tests of bile microRNA during ERCP mayraise the diagnostic value of the approach in questionable results regarding the degree of cholestasis.

THERAPEUTIC POSSIBILITIES OF MICRORNA

Many studies demonstrate the important regulatory role of miRNA [15, 18, 20, 25, 28]. Such regulatory properties give the microRNA a high therapeutic potential. Currently, there are studies confirming the possibility of using miRNA as a therapeutic agent [28]. Thus, injections of miR-122 in patients with cholangiocarcinoma also significantly reduced the intensity of the inflammatory process and suppressed the proliferation of the tumor [15]. Inhibition of miR-122 in hepatitis C can reduce the level of viremia and improve the functional state of the liver [15].

Concerning cholestatic injury, it was shown that blocking the miR-21 gene in mice significantly reduced the intensity of hepatocyte necrosis due to ligation of the common bile duct [28]. This may indicate that miR-21 is among the first to respond to acute cholestasis and triggers pathological changes in the liver. In other studies, Yang Y. L. et al., Tiao M. M. et al. obtained similar results due to the inhibition of miR-29a activity [26].

CONCLUSIONS

Concomitant choledocholithiasis in acute calculous cholecystitis requires surgical treatment along with cholecystectomy. The diagnosis of cholestasis induced by choledocholithiasis in acute cholecystitis is a complex and cost-ineffective task often requiring the use of invasive ERCP. Basic biochemical tests, such as aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, have low specificity and sensitivity in relation to the diagnosis of choledocholithiasis in acute cholecystitis.

The microRNA can be used as an additional method for diagnosing choledocholithiasis in cholecystitis if conventional approaches do not provide comprehensive information on the state of the hepatobiliary system of a patient at the preoperative stage. Simultaneous quantitative and qualitative test of the microRNA profiles in bile and plasma has a combination of high sensitivity and specificity in the diagnosis of benign cholestasis in acute calculous cholecystitis. Moreover, the test enables a differential diagnosis with other cholestatic diseases, mostly of a neoplastic nature.

Further studies of miRNAs in both plasma and bile are required to create a greater evidence base and identify the most specific type of microRNA for acute benign cholestasis, namely choledocholithiasis.

REFERENCES

1. Costi R, Gnocchi A, Di Mario F et al. Diagnosis and management of choledocholithiasis in the golden age of imaging, endoscopy and laparoscopy . World J Gastroenterol. 2014;20(37):13382-401. doi: 10.3748/wjg.v20.i37.13382. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25309071
2. Gurusamy KS, Giljaca V, Takwoingi Y et al. Ultrasound versus liver function tests for diagnosis of common bile duct stones. Cochrane Database Syst Rev. 2015;2:CD011548. doi: 10.1002/14651858.CD011548. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25719223
3. Tazuma S, Unno M, Igarashi Y et al. Evidence-based clinical practice guidelines for cholelithiasis . J Gastroenterol. 2017;52(3):276-300. doi: 10.1007/s00535-016-1289-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27942871
4. Joyce WP, Keane R, Burke GJ et al. Identification of bile duct stones in patients undergoing laparoscopic cholecystectomy. Br J Surg. 1991;78(10):1174-6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/1835665
5. Marin JJ, Bujanda L, Banales JM. MicroRNAs and cholestatic liver diseases. Curr Opin Gastroenterol. 2014;30(3):303-9. doi: 10.1097/MOG.0000000000000051. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24553410
6. Yamaura Y, Nakajima M, Takagi S et al. Plasma MicroRNA Profiles in Rat Models of Hepatocellular Injury, Cholestasis, and Steatosis. PLoS One. 2012;7(2):e30250. doi: 10.1371/journal.pone.0030250. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0030250
7. Wang XW, Heegaard NHH, Orum H. MicroRNAs in Liver Disease. Gastroenterol. 2012;142(7):1431-43. doi: 10.1053/j.gastro.2012.04.007. Available from: https://www.sciencedirect.com/science/article/pii/S0016508512005100
8. Buzas EI, György B, Nagy G et al. Emerging role of extracellular vesicles in inflammatory diseases. Nat Rev Rheumatol. 2014;10(6):356-64. doi: 10.1038/nrrheum.2014.19. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24535546
9. Th'ng F. Role of microRNA biomarkers to predict complications of gallstones. MD thesis. The University of Edinburgh. 2015. Available from: https://www.era.lib.ed.ac.uk/handle/1842/18012?show=full
10. Kagawa T, Shirai Y, Oda S et al. Identification of Specific MicroRNA Biomarkers in Early Stages of Hepatocellular Injury, Cholestasis, and Steatosis in Rats. Toxicol Sci. 2018;166(1):228-39. doi: 10.1093/toxsci/kfy200. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30125006
11. Woolbright BL, Antoine DJ, Jenkins RE et al. Plasma biomarkers of liver injury and inflammation demonstrate a lack of apoptosis during obstructive cholestasis in mice. Toxicol Appl Pharmacol. 2013;273(3):524-31. doi: 10.1016/j.taap.2013.09.023. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24096036
12. Shifeng H, Danni W, Pu C et al. Circulating liver-specific miR-122 as a novel potential biomarker for diagnosis of cholestatic liver injury. PLoS One. 2013;8(9):e73133. doi: 10.1371/journal.pone.0073133. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24086271

13. Yang YL, Wang FS, Li SC et al. MicroRNA-29a Alleviates Bile Duct Ligation Exacerbation of Hepatic Fibrosis in Mice through Epigenetic Control of Methyltransferases. Int J Mol Sci. 2017;18(1)192. doi: 10.3390/ijms18010192. Available from: https://www.mdpi.com/1422-0067/18/1/192/html
14. Oda S, Takeuchi M, Akai S et al. miRNA in Rat Liver Sinusoidal Endothelial Cells and Hepatocytes and Application to Circulating Biomarkers that Discern Pathogenesis of Liver Injuries. Am J Pathol. 2018;188(4):916-28. doi: 10.1016/j.ajpath.2017.12.007. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29353062
15. Hsu S, Wang B, Kota J et al. Essential metabolic, anti-inflammatory, and anti-tumorigenic functions of miR-122 in liver. J Clin Invest. 2012;122(8):2871-83. doi: 10.1172/JCI63539. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3408748/
16. Cheung AC, Lorenzo Pisarello MJ, LaRusso NF. Pathobiology of biliary epithelia. Biochim Biophys Acta Mol Basis Dis. 2018;1864(4 Pt B):1220-31. doi: 10.1016/j.bbadis.2017.06.024. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28716705
17. Bessho K, Shanmukhappa K, Sheridan R et al. Integrative genomics identifies candidate microRNAs for pathogenesis of experimental biliary atresia. BMC Syst Biol. 2013;7:104. doi: 10.1186/1752-0509-7-104. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24138927
18. Schaap FG, Soons Z, Fischer L et al. Large Scale Alterations in Hepatic MRNA and MIRNA Expression in Human Extrahepatic Cholestasis. J Hepatol. 2016;64(2 Suppl):S437-8. doi: 10.1016/S0168-8278(16)00719-4. Available from: https://www.journal-of-hepatology.eu/article/S0168-8278(16)00719-4/abstract
19. Glaser S, Meng F, Han Y et al. Secretin stimulates biliary cell proliferation by regulating expression of microRNA 125b and microRNA let7a in mice. Gastroenterology. 2014;146(7):1795-808. doi: 10.1053/j.gastro.2014.02.030. Availablefrom: https://www.ncbi.nlm.nih.gov/pubmed/24583060
20. Verhoeven CJ, Farid WR, Roest HP et al. Polarized release of hepatic microRNAs into bile and serum in response to cellular injury and impaired liver function. Liver Int. 2016;36(6):883-92. doi: 10.1111/liv.12955. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26344705
21. Gradilone SA, O'Hara SP, Masyuk TV et al. MicroRNAs and benign biliary tract diseases. Semin Liver Dis. 2015;35(1):26-35. doi: 10.1055/s-0034-1397346. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25632932
22. Verhoeven CJ, Metselaar HJ, Van der Laan LJV. Barking up the wrong tree: MicroRNAs in bile as markers for biliary complications. Liver transplant. 2014;20:637-9. doi: 10.1002/lt.23898. https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/lt.23898
23. Th'ng F, Vliegenthart B, Lea JD et al. Biomarker evaluation of plasma microRNA-122, high-mobilitygroup box-1 and keratin-18 in acute gallstone disease. BioRxiv. 2017; doi: 10.1101/189589. Availablefrom: https://www.biorxiv.org/content/early/2017/09/16/189589
24. Kennedy LL, Meng F, Venter JK et al. Knockout of microRNA-21 reduces biliary hyperplasia and liver fibrosis in cholestatic bile duct ligated mice. Lab Invest. 2016;96:1256-67. doi: 10.1038/labinvest.2016.112. Available from: https://www.nature.com/articles/labinvest2016112
25. Kishimoto T, Eguchi H, Nagano H et al. Plasma miR-21 is a novel diagnostic biomarker for biliary tract cancer. Cancer Sci. 2013;104(12):1626-31. doi: 10.1111/cas.12300. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24118467
26. Tiao MM, Wang FS, Huang LT et al. MicroRNA-29a protects against acute liver injury in a mouse model of obstructive jaundice via inhibition of the extrinsic apoptosis pathway. Apoptosis. 2014;19(1):30-41. doi: 10.1007/s10495-013-0909-4. Available from: https://link.springer.com/article/10.1007/s10495-013-0909-4
27. Lankisch TO, Voigtländer T, Manns MP et al. MicroRNAs in the bile of patients with biliary strictures after liver transplantation.. Liver Transpl. 2014;20(6):673-8. doi: 10.1002/lt.23872. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24648209
28. Afonso MB, Rodrigues PM, Simão AL et al. miRNA-21-deficiency reduces liver injury, fibrosis and necroptosis in cholestatic bile duct-ligated mice. J Hepatol. 2017;66(1):S555. doi: 10.1016/S0168-8278(17)31522-2. Available from: https://www.journal-of-hepatology.eu/article/S0168-8278(17)31522-2/abstract
29. Severino V, Dumonceau JM, Delhaye M et al. Extracellular Vesicles in Bile as Markers of Malignant Biliary Stenoses. Gastroenterology. 2017;153(2):495-504. doi: 10.1053/j.gastro.2017.04.043. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28479376

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Oleg M. Terletskiy
Department of Surgery № 1,
Lviv Danylo Halytsky National Medical University
Pecarskaya str., 69, 79010 Lviv, Ukraine
tel: + 380974655895
e-mail: olegterletskiy@ukr.net

Received: 04.03.2019
Accepted: 12.06.2019

OPIS PRZYPADKU
CASE REPORT

REHABILITATION OF INFANTS AFTER TRANSTIBIAL AMPUTATION DUE TO THROMBOSIS IN THE PERINATAL PERIOD. CASE REPORT

REHABILITACJA NIEMOWLĄT PO AMPUTACJI PODUDZIA Z POWODU ZAKRZEPICY W OKRESIE OKOŁOPORODOWYM. OPIS PRZYPADKU

Agnieszka Strączyńska, Agnieszka Radzimińska, Magdalena Weber-Rajek, Katarzyna Strojek, Zuzanna Piekorz, Aleksander Goch
DEPARTMENT OF PHYSIOTHERAPY, NICOLAUS COPERNICUS UNIVERSITY IN TORUN, COLLEGIUM MEDICUM IN BYDGOSZCZ, BYDGOSZCZ, POLAND

ABSTRACT

Congenital thrombosis and amputation in infancy is not common. Therefore, the existing literature lacks sufficient evidence regarding this subject. Available research primarily focuses on treatment and causes of thrombosis in children. The paper describes a case of preterm infant after transtibial amputation due to common iliac artery thrombosis during the perinatal period. The girl began neurodevelopmental therapy based on normal development patterns of infants, which was provided three times a week for 45 minutes. The rehabilitation process also included prosthesis and surgical interventions. The assessment of motor development of the child was carried out at the age of 6, 9, 12, 18 and 20 months, using the motor scale of the Albert Infants Motor Scale (AIMS). Case analysis allows to state that infant rehabilitation after transtibial amputation should be individualized, and focus on supporting normal motor development, based on the correct movement sequences of infants. Additionally, the AIMS scale can be used to assess the gross motor development in infants after amputation and is useful in formulating early therapeutic intervention. A prosthetist should perform prosthesis revisions as often as needed, i.e., in infants that is usually every 4 months. What is more, successful outcomes can be achieved by implementing proper surgical procedures regarding the appositional overgrowth of the residual limb in growing children.

KEY WORDS: congenital thrombosis, amputation in infants, rehabilitation

STRESZCZENIE

Wrodzona zakrzepica i amputacje w okresie niemowlęcym nie są powszechnie spotykane. Dlatego również w istniejącej literaturze brakuje wystarczających informacji dotyczących tego tematu. Dostępne badania skupiają się przede wszystkim na leczeniu i przyczynach zakrzepicy u dzieci. W pracy opisano przypadek wcześniaka po amputacji podudzia z powodu zakrzepicy tętnicy biodrowej wspólnej w okresie okołoporodowym, który uczestniczył w terapii neurorozwojowej, trzy razy w tygodniu przez 45 minut. Proces usprawniania dotyczył również protezowania oraz interwencji chirurgicznych. Ocenę rozwoju motorycznego dziecka przeprowadzono w wieku 6, 9, 12, 18 i 20 miesięcy, stosując skalę motoryczną Alberta Infants Motor Scale (AIMS). Analiza przypadku pozwala stwierdzić, iż rehabilitacja niemowląt po amputacji powinna być zindywidualizowana i skoncentrowana na wspieraniu prawidłowego rozwoju motorycznego, w oparciu o prawidłowe sekwencje ruchowe niemowląt. Dodatkowo, skala AIMS może być wykorzystana do oceny ogólnego rozwoju motorycznego u niemowląt po amputacji i jest przydatna w formułowaniu wczesnej interwencji terapeutycznej. Protetyk powinien przeprowadzać rewizje protez tak często, jak jest to konieczne, u niemowląt co 4 miesiące. Co więcej, pozytywne wyniki usprawniania można osiągnąć poprzez wdrożenie odpowiednich procedur chirurgicznych dotyczących apozycyjnego przerostu kikuta u dzieci w okresie wzrastania.

SŁOWA KLUCZOWE: wrodzona zakrzepica, amputacje u niemowląt, rehabilitacja

Wiad Lek 2019, 72, 7, 1408-1412

INTRODUCTION

Lower limb amputation in children is relatively uncommon and there is scarce knowledge regarding the rehabilitation process for this population. In fact, most of the available literature focuses on adults. Some key information about rehabilitation may be transferable to children, but there are significant differences in the rehabilitation processes of pediatric and adult patients after amputation. These differences are influenced by the etiology of limb loss, motor development evaluation, bone growth, appositional overgrowth of the residual limb bone and functional prosthetic supply [1–3].

The most frequent indications for major lower limb amputations are traumatic injury, congenital limb deficiencies, severe infections, tumors, and vascular abnormalities (vasculitis and vascular malformation) [4].

The etiology of thrombosis in children is not fully understood. However, the factors causing or increasing the risk of thrombosis are clearly identified. The available research has shown a connection between the occurrence

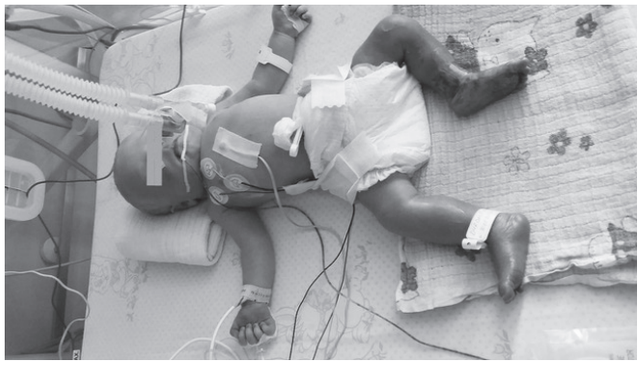


Fig. 1. The image of the girl's condition on the second day of life at the Intensive Care Unit and the Neonatal Pathology Unit

of thrombosis and inherited thrombophilia, deficiency of proteins C and S and antithrombin, as well as factor V Leiden gene mutation [5]. Other predisposing factors are infection, surgery, congenital heart defects, injuries, nephrotic syndrome, systemic lupus erythematosus, cancer and complications from its treatment (the presence of central catheter) [6]. Symptoms of thrombosis in children may differ depending on the thrombus size, location, and cause. The changes mainly concern the lower limb vascular system, though thrombosis may also develop in other organs, such as lungs, liver, and kidneys [7]. Lower limb thrombosis causes pain near the affected extremity, in the groin or in the abdomen. Additionally, there is swelling and reddish-purple discoloration of the skin. Prolonged ischemia can lead to trophic changes in tissue, resulting in necrosis. Ischemia may be life-threatening to children; that is why treatment methods include amputation of the afflicted limb [8]. Statistically, amputation is rare, but it can occur even as early as in infancy [1]. Surgical amputation of lower limbs in children differs from amputation in adults. General principles of amputation surgery in children are saving growth plates, performing disarticulation rather than trans osseous amputation, and preserving the knee joint, if possible [9]. Regardless of age, a properly executed surgery and the stump shape are crucial factors which maximize the immediate and future outcomes for the patient [10].

CASE PRESENTATION

This case report documents the assessment and rehabilitation of a girl born by caesarean section at gestational week 34. Her birth weight was 2680 g and she presented with an Apgar score of 8/10. At day one, she was admitted to the Intensive Care Unit and the Neonatal Pathology Unit due to suspected thrombosis in the left lower limb and respiratory failure. Both lower limbs were swollen, and there was reddish-purple skin discoloration (Fig. 1).

A thrombosis was diagnosed in the left common external iliac artery, and subsequent changes in the left femoral artery and the umbilical artery were detected using Doppler ultrasound. Initial treatment included heparin, pentoxifylline, and topical medication. On the third day of life, limb involvement was limited to the foot and the 1/3 distal part of the left leg. After eight days of conservative treatment, and due to necrotic lesions, the risk of sepsis, and the need for higher level amputation, surgeons decided to perform a transtibial amputation. No complications arose during surgery and the entire perioperative period. The girl was discharged after a month and a half of hospitalization following birth. At the age of 7 months, the girl was readmitted to the Department of Pediatric Surgery to undergo correction surgery of the left residual limb due to bone overgrowth. The bone overgrowth has been treated using conventional practice, i.e., a resection of the overlying bursa and shortening of the bone stump. As expected, there were no complications during the intra- and perioperative periods. After a three-day hospitalization, the child was discharged. Once wound healing occurred, the girl was fitted with the first temporary prosthesis, and rehabilitation was initiated.

INITIAL EXAMINATION

At the age of 6 months, the girl was examined by a physical therapist. Due to the lack of standardized developmental scale for children after amputation, the girl's motor development was assessed using the Alberta Infant Motor Scale (AIMS) intended to assess motor development of healthy children. This screening tool is designed to examine, discriminate, and evaluate the movement of infants from birth to independent walking, and it is useful for monitoring gross motor developmental changes in the first 18 months of life. The AIMS also provides reliable and valid measurements in preterm infants [11]. The scale identifies components of dynamic movement by observing infants as they move into and out of four positions: prone, supine, sitting, and standing. Moreover, the AIMS scale is very efficient as it takes only 20 minutes to fill out the questionnaire and assess developmental changes in a child, both in quantitative and qualitative terms [12]. The observation of spontaneous movements was carried out at 6, 9, 12, 18, and 20 months of age. The AIMS is intended to evaluate normal development of infants. Meanwhile, the authors used the scale to assess the girl's development and to determine the main therapy goals. The therapeutic intervention was designed based on accurate descriptions of movement sequences expected at a certain month of life.

DESCRIPTION OF THE INTERVENTION

When the girl was 6 months old, rehabilitation services were provided three times a week for 45 minutes. Neurodevelopment therapy based on the NDT-Bobath concept and normal development patterns of infants was used to learn the correct movement sequences. At the age of 8 months, the girl received her first temporary prosthesis. Once the prosthesis was prepared, the parents were trained on how to use it daily as well as how to encourage the child to use it. The girl faced difficulties adjusting to the prosthesis especially during the crawling stage because it often slipped off the residual limb upon hitting a piece of furniture or another obstacle. At 14 months, when the girl could pull up to a sitting position and

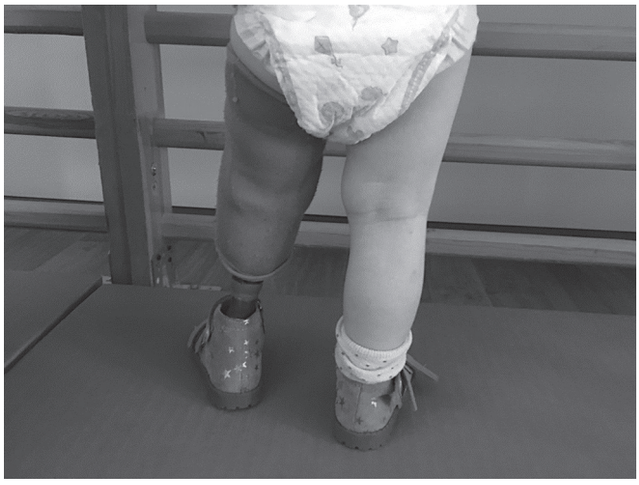


Fig. 2. The second temporary prosthesis with a stocking for the residual limb

Fig. 3. The postoperative scar on the left residual limb

assume weight bearing in quadruped position, her balance and equilibrium reactions were deemed appropriate, and she was finally ready to stand while wearing the temporary prosthesis. Standing practice was performed at the couch, with fully extended hips and knees (without hyperextension), and a maintained alignment between the femur and tibia. During the therapy, at 14 months of age, the girl was taught how to use the prosthesis correctly in a standing position. She was given opportunities to develop side forward and backward stepping patterns. At the age of 18 months, due to the body growth the child was fitted with a new prosthesis with an additional silicone sleeve (Fig. 2).

At 18 months of age, the girl started to learn an alternating step-through gait pattern with the use of a posterior walker. At the age of 20 months, the girl began to take first independent steps without any equipment. During this rehabilitation phase, the girl experienced a complication and had to discontinue the therapeutic intervention. Appositional bone growth of the left tibia began to bulge at the bottom of the residual limb (Fig. 3).

During the whole therapy period, the girl's parents were actively involved in the rehabilitation process. Their key role was to encourage the girl to regularly wear the prosthesis or belay her with daily activities, such as getting up or using the posterior walker.

THE APPOSITIONAL BONE OVERGROWTH AND SURGICAL INTERVENTIONS

The first surgical intervention took place at the age of 7 months. At first, the girl felt stump pain when too much pressure was applied on the stump in the standing position. She suddenly began to cry during every day play. At the age of 7 months, a small skin perforation appeared on the top of the residual limb. This was caused by a bony spike which has formed at the end of the tibia. The girl's parents also reported that the child woke up at night crying and pointing to the stump. The girl was referred to an orthopedist by the physical therapist. Then the girl underwent a surgical revision (capping of the medullary canal along with resection of the bony spike) which is necessary to correct growth disorders.

At the age of 20 months, the scar shifted to the middle of the stump and the surrounding soft tissues were flattened due to bone growth. The first signs of residual limb issues were manifested as the girl's reluctance to put on and wear the prosthesis. Most likely weight bearing on the left side of the body resulted in pain, which the girl communicated with crying. These changes in the residual limb disrupted correct weight bearing, proper prosthesis use, and the girl's tolerance of the prosthesis. Surgical resection was repeated after an orthopedic consultation. The girl will certainly receive a new prosthesis and once the wound is healed, she will return to the standing position and continue learning the correct gait.

DESCRIPTION OF THE NEURODEVELOPMENTAL OUTCOME

Gross motor function was evaluated six times for corrected age (CA) using the AIMS. The outcome measurements are presented in Table I.

For comparative purposes, during the last functional exam using the AIMS scale, the child was provided with a below-the-knee prosthesis. Since the girl was born at 34-week gestation, her scores on the AIMS are for her corrected age. Her corrected age was adjusted by 6 weeks or 1.5 months (the child's gestational age of 34 weeks was subtracted from a 40-week full-term). At the 6-month measurement, the girl obtained a total score of 23 and a percentile rank of 50%, which indicates that the patient demonstrated typical motor development for her adjusted age. At 4.5 months CA, the girl was able to roll supine to prone, lift, and also maintain head past 45^0 and controlled reach with free arms in prone position. The girl also reached hands to knees due to active abdominals and proper pelvic mobility in the supine position. In subsequent gross motor performance measurements, the girl's total score increased, but her skills were not age-appropriate. Therefore, the percentile range diminished with age in subsequent studies. At 7.5 months CA, additionally, she learned to pivot in the prone position and to sit with arm support. At 10.5 months CA, the girl used half-sitting and was

Table I. Alberta Infant Motor Scale (AIMS) subscale and total scores.

AIMS subscales and total score	6 months old (4.5 months CA)	9 months old (7.5 months CA)	12 months old (10.5 months CA)	18 months old (16.5 months CA)	20 months old (18.5 months CA)	20 months old with a prosthesis (18.5 months CA)
Prone	11	12	16	18	21	21
Supine	8	9	9	9	9	9
Sitting	3	5	12	12	12	12
Standing	1	1	2	6	9	14
Total score	23	27	39	45	51	56
Percentile	50%	25%	5%	<5%	<5%	<5%

CA – corrected age; TH-percentile

able to roll prone to supine, crawl, and sit without arm support. At 16.5 months CA, she was able to creep, pull to stand, stand with arm support and without prosthesis, and move to the side by jumping on one leg with support. At the age of 20 months (18.5 months CA), the girl reached maximum results in the prone, supine, sitting and standing subscales. At 20 months, the girl's percentile rank dropped significantly due to the fact that the child was not able to walk. During the 20-month evaluation, the child obtained higher scores when using the below-the-knee prosthesis. The device encouraged the patient to shift weight from side to side, cruise sideways, control lowering through standing, and stand alone. But most importantly, the girl was able to take several independent steps using a posterior walker.

Usually, the AIMS is intended to evaluate normal development of infants. However, in case of this study the scale was used not only to assess the girl's development but also constituted the basis for determining the main therapy goals.

DESCRIPTION OF THE PROSTHETIC MANAGEMENT

At the age of 8 months, the girl received her first temporary below-the-knee prosthesis. The device was supposed to help the infant develop tolerance to the prosthesis, as well as support the development of a correct body map and a normal sensorimotor experience. The prosthesis was not equipped with a mechanical suspension mechanism proximal to the condyles, which means that it allowed typical development of quadriceps, without any reduction of muscle mass or the residual limb circumference [13]. At the age of 14 months, when the girl learned how to get up and use side walking, she received a modular prosthesis with a single axis foot. At 18 months, following another consultation with the prosthetist, the prosthesis socket was replaced by a bigger one due to increased circumference of the residual limb. Additionally, a silicone sleeve was used to control tightening over the stump. It allowed the stump to adhere and compress soft tissues into the shape required to accommodate the rigid socket. The silicone sleeve kept the prosthesis socket on the residual limb in a stable position and prevented it from slipping off during dynamic movements while learning to walk.

The protheses were designed and manufactured using a traditional cast method. The prosthetist followed up with the girl regularly every 4 months to ensure that the device was still adjusted to the child's growing body. Changes in residual limb length and volume were monitored during the follow-up visits. The physical therapist was also in constant contact with the prosthetist, who controlled the quality of the prosthesis in use.

DISCUSSION

Thrombosis rarely appears during the neonatal period. Unfortunately, the necessary treatment results in surgical removal of the affected tissue. The available published studies indicate that around 42% of cases of limb thrombosis in infants ended up with amputation [8,14,15]. These surgeries were life-saving. Children with amputations should receive good care before and after surgery. The patients should be fitted with a prosthesis and afterwards receive a long-term rehabilitation. It should be noted that the surgical team makes extremely important decisions about the level of amputation [16]. Another factor which plays an essential role in prosthesis selection is the scar placement on the stump. The prosthesis socket should not press against the scar. Furthermore, prosthesis fitting should occur as fast as possible and it usually occurs in 8 month old infants as its lack significantly impacts the child's functional development [17]. Properly selected prosthesis supports maximum function, symmetry, and the development of a correct body map [18]. Choosing the right prosthesis is a big challenge for prosthetists, because the residual limb of a child is still growing and changing. Moreover, the type of prosthesis depends on an infant's dynamic development of various movement skills, such as walking on all fours or standing up [19].

At the time this case report was created, no research was available to guide the authors on how to assess the development of a premature infant after amputation of a lower limb. The existing literature does not indicate any proper assessment tools which should be used to measure both quantitative and qualitative changes in gross motor skill development. The AIMS is a free tool that allows quick and accurate assessment of motor development in premature infants [12,20]. There are many tools which could be used to evaluate a child's development, such as the Movement Assessment of Infants (MAI) [21], the Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT) [22], or the Peabody Developmental Gross Motor Scale (PDMS-GM) [23]. However, if any of these tools were

used, then the research would have been more time-consuming and expensive.

Furthermore, the most significant post-surgical complication described in the rehabilitation process was the appositional bone overgrowth, which caused skin perforation, and consequently made it difficult to cure. As a result, only a greater number of surgical revisions may prevent the appositional overgrowth in the residual limb, and it may be possible to change the surgical procedure during the subsequent reoperation to affect the improvement process itself [16,24]. Appositional overgrowth of the residual limb occurs in 4% to 35% of children and is most common in below-knee amputation [16]. In every case, revision surgery may prove necessary, particularly to correct growth disorders. The child and parents should be informed of this possibility.

The purpose of physical rehabilitation of infants after amputation is to provide them with a new experience through achieving correct motor sequences expected during infancy. It is also equally important to properly educate parents on supporting the development of a small child and encouraging them to accept the prosthesis and becoming more independent in numerous real-life situations.

CONCLUSIONS

Based on this case description, the AIMS scale can be used to assess the gross motor development in infants after amputation and is useful in formulating early therapeutic intervention. The approach to infants after transtibial amputation should be individualized, and focus on supporting normal motor development, based on the correct movement sequences of infants. Prosthesis revisions should be performed as often as needed, i.e., in infants that is usually every 4 months. What is more, successful outcomes can be achieved by implementing proper surgical procedures regarding the appositional overgrowth of the residual limb in growing children.

REFERENCES

1. de Godoy JMP, de Godoy LMP. Epidemiological Data of Amputations in Children. Clin Pediatr Dermatol. 2016;2(8):1-3.
2. Smith DG, Michael JW., Bowker JH et al. Atlas of amputations and limb deficiienes: surgical, prosthetic and rehabilitation principles. 3 rd edition. Rosemont (IL): American Academy of Orthopedic Surgeons. 2004;773-914.
3. Cummings DR. Pediatric prosthetics. Current trends and future possibilities. Phys Med and Rehabil Clin N Am. 2000; 1:653-679.
4. Banza LN, Mkandawire NC, Harrison WJ. Amputation surgery in children: an analysis of frequency and cause of early wound problems. Trop Doct.2009;39:129-132.
5. David M, Manco-Johnson M, Andrew M Diagnosis and treatment of venous thromboembolism in children and adolescents. On behalf of the Subcommittee on Perinatal Haemostasis of the Scientific and Standardization Committee of the ISTH. J Thromb Haemost 1995;74:791.
6. Chalmers EA. Neonatal thrombosis. J Clin Pathol. 2000;53419-23.
7. Chalmers E, Ganesen V, Liesner R. et al. Guideline on the investigation, management and prevention of venous thrombosis in children.Br J Haematol. 2011;154:196.
8. Arshad A, McCarthy MJ. Management of limb ischemia in the neonate and infant. Eur J Vasc Endovasc Surg. 2009;38:61-65.
9. Krajbich JI. Lower-limb deficiencies and amputations in children. J Am Acad Orthop Surg. 1998;6:358-367.
10. Khan MAA, Javed AA, Rao DJ et al. Pediatric traumatic limb amputation: the principles of management and optimal residual limb lengths. W J Plast Surg 2016;5:7-14.
11. Piper MC, Darrah J 1994 Motor assessment of the developing infant. Philadelphia: WB Saunders
12. Diarrah J, Piper M, Watt MJ. Assessment of gross motor skills of at-risk infants: predictive validity of the Alberta Infant Motor Scale. Deve Me Child Neurol 1998;40:485-491.
13. Griffet J. Amputation and prosthesis fitting in paediatric patients. Orthop Traumatol Surg Res 2016;102:161-175.
14. Farrar MJ, Bennet GC, Wilson NIL et al. The orthopaedic implications of peripheral limb ischemia in infants and children. Bone Joint J. 1996;8:930-933.
15. Rasool MN, Pryce-Lewis J, Smit R. Ischaemia of the foot in infants. SA Orthop J. 2009;8(4):72-75.
16. Westberry DE. State of the Art: Amputation and Prosthetics. J Pediatr Orthop 2017;37:22-25.
17. Le JT, Scott-Wyard PR. Pediatric limb differences and amputations. Phys Med Rehabil Clin Am 2015;26:95-108
18. Cummings DR, Kapp SL. Lower-limb pediatric prosthetics: general considerations and philosophy. J Prosthet and Orthot. 1992;4:196-206.
19. Cummings DR. Pediatric prosthetics: an update. Current trends and future possibilities. Phys Med Rehabil Clin Am 2000;17:15-21.
20. vanHaastert IC, de Vries LS, Helders PJ et al. Early gross motor development of preterm infants according to the Alberta Infant Motor Scale. J Pediatr 2006;149:617-622.
21. Campbell SK, Zawacki L, Rankin KM et al. Concurrent validity of the TIMP and the Bayley III scales at 6 weeks corrected age. Pediatr Phys Ther 2013;25(4):395-401.
22. Haley SM, Coster WI, Kao YC et al. Lessons from use of the Pediatric Evaluation of Disability Inventory: where do we go from here? Pediatr Phys Ther 2010;22:69-75.
23. Palisado RJ, Kolobe TH, Haley SM, et al. Validity of the Peabody Developmental Gross Motor Scale as an Evaluative Measure of Infants Receiving Physical Therapy. Phys Ther 1995;11:939-951.
24. Vocke AK, Schmid A. Osseous overgrowth after post-traumatic amputation of the lower extremity in childhood. Arch Orthop Trauma Surg. 2000;120:452-454.

Conflict of interest:
The authors declare no conflict of interest.

CORRESPONDING AUTHOR

Agnieszka Strączyńska
Department of Physiotherapy; Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Poland;
3 Techników Street; 85-801 Bydgoszcz, Poland
e-mail: a.straczynska@icloud.com

Received: 26.03.2019
Accepted: 16.05.2019

OPIS PRZYPADKU
CASE REPORT

PRZYPADEK RZADKIEGO NOWOTWORU NEUROGENNEGO KRTANI

A CASE OF RARE LARYNGEAL NEUROGENIC TUMOR

Jacek Czubak, Marcin Frączek, Krzysztof Morawski
KLINIKA OTOLARYNGOLOGII, CHIRURGII GŁOWY I SZYI UM WE WROCŁAWIU, WROCŁAW, POLSKA

STRESZCZENIE

Schwannoma (nerwiak osłonkowy) należy do rzadkich nowotworów krtani. Powstaje z komórek Schwanna. Badanie rezonansu magnetycznego (MR) jest najlepszym badaniem obrazowym w diagnostyce tego nowotworu. Prezentujemy przypadek nerwiaka osłonkowego krtani. Przypadek to 61-letni pacjent z rocznym wywiadem chrypki i duszności. W laryngoskopii uwidoczniono gładkościenny guz okolicy głośni. Tomografia komputerowa pokazała masę o wymiarach 26(CC) x 18 (TR) x 24 (AP) mm szerzącą się w okolicy głośni. Histopatologicznie potwierdzono rozpoznanie nerwiaka. U pacjenta wykonano radykalny zabieg operacyjny z dojścia zewnątrzkrtaniowego. W pracy przedyskutowano diagnostykę oraz metody leczenia.

SŁOWA KLUCZOWE: *Schwannoma, Neurilemmoma,* nerwiak osłonkowy krtani

ABSTRACT

Laryngeal schwannoma is a rare benign tumour of the larynx. Schwannomas derive from the Schwann cells. Magnetic resonance imaging (MRI) is the best imaging tool for suggesting the diagnosis. We report case of laryngeal schwannoma. The case was a 61-year-old man with a 1-year history of dysphonia and stridor. Laryngoscopy revealed a submucosal mass of the glottic area. A computed tomography scan of the larynx showed an 26(CC) x 18 (TR) x 24 (AP)mm expansile mass in the glottic area. Histopathological examination diagnosed a schwannoma of the larynx. External surgeries were successfully performed. Diagnosis and specific treatment are discussed.

KEY WORDS: *Schwannoma, Neurilemmoma*, Larynx

Wiad Lek 2019, 72, 7, 1413-1414

WSTĘP

Nowotwory neurogenne stanowią 2% guzów (z wyłączeniem guzów n.VIII) regionu głowy i szyi [8]. W ponad 50% są to nowotwory wywodzące się z nerwów obwodowych [8]. Nerwiak osłonkowy (inaczej *Schwanomma, Neurilemmoma*) stanowi 45–50% tej grupy [8]. Ten łagodny nowotwór osłonek nerwów obwodowych lokalizuje się najczęściej w przestrzeni przygardłowej [2]. Nerwiak osłonkowy umiejscowiony w krtani jest rzadkim guzem, częstość jego występowania w tej lokalizacji to jedynie 0,1–1,5% wszystkich łagodnych nowotworów krtani [2]. Powstaje z osłonek wewnętrznej gałęzi nerwu krtaniowego górnego i częściej występuje u kobiet między 4. a 5. dekadą życia [2]. Jedynym znanym czynnikiem zwiększającym ryzyko wystąpienia tego nowotworu jest przebyta radioterapia [2]. Morfologicznie nerwiak osłonkowy jest rosnącym powoli (od 2,5 mm do 3 mm na rok) twardym, otorebkowanym guzem [1, 2]. Objawy guza są niecharakterystyczne: stridor, chrypka, dysfagia, odynofagia, duszność oraz pojawiają się dopiero, gdy zmiana osiąga duże rozmiary [2]. Rzadko dochodzi do złośliwej transformacji w złośliwego nerwiaka osłonkowego (*Schwanomma malignum*) [8].

Rozpoznanie ustala się na podstawie badań obrazowych tomografii komputerowej (TK) lub rezonansu magnetycznego (MR) oraz badania histologicznego. Histopatologicznie istotne znaczenie mają trzy kryteria: utkanie nowotworu, w którym komórki są zbite i ustawione palisadowato (Antoni A) i utkanie, w którym komórki są ułożone nieregularnie i luźno (Antoni B) oraz ekspresja białka S-100 [1, 2].

W artykule przedstawimy przypadek 61-letniego mężczyzny z łagodnym nerwiakiem osłonkowym krtani.

OPIS PRZYPADKU

Mężczyzna lat 61 został przyjęty w trybie pilnym do Kliniki Otolaryngologii, Chirurgii Głowy i Szyi we Wrocławiu z powodu guza krtani. Pacjent od roku skarżył się na nasilającą się chrypkę, duszność oraz dysfagie**.** Pacjent niepalący papierosów, bez chorób przewlekłych, nienarażony zawodowo na czynniki toksyczne.

W wykonanej laryngoskopii pośredniej stwierdzono gładkościenny guz zwężający znacząco światło szpary głośni, z prawidłową ruchomością strun głosowych.

W wykonanym badaniu TK uwidoczniono zmianę wielkości około 26(CC) x 18(TR) x 2(AP) mm, który szerzył się w obrębie głośni i podgłośni z lokalną infiltracją przestrzeni

błony śluzowej gardła dolnego. Guz uciskał i przemieszczał przyśrodkową chrząstkę nalewkowatą, znacznie zwężając światło głośni i w mniejszym stopniu światło podgłośni. Nie wykazano limfadenopatii (Ryc. 1)

U pacjenta z uwagi na narastającą duszność wykonano ratunkową tracheotomię oraz pobrano wycinek z guza. W badaniu histopatologicznym uwidoczniono charakterystyczne dla nerwiaka osłonkowego utkanie komórek (Antoni A oraz Antoni B). Następnie po 2 tygodniach pacjent został przyjęty celem operacji. Z uwagi na duży rozmiar zmiany wykonano zabieg doszczętnego usunięcia guza z dostępu zewnątrzkrtaniowego przez tyreotomię pośrodkową. Pacjent został wypisany do domu w drugiej dobie po zabiegu.

W wykonanej po 3 tygodniach kontrolnej laryngoskopii pośredniej uwidoczniono szeroką szparę głośni oraz prawidłową ruchomość strun głosowych. Pacjenta dekaniulowano i zeszyto tracheostomie. Pacjent zgłosił się ponownie po 3 miesiącach celem kolejnej laryngoskopii pośredniej w obrazie, której nie zaobserwowano wznowy guza. Po 8 miesiącach pacjent poddany Rezonansowi Magnetycznemu (MR) krtani, gdzie również nie stwierdzono obecności zmian świadczących o nawrocie choroby.

DYSKUSJA

Guz typu Schwanomma jest rzadkim nowotworem łagodnym krtani. Stanowi 0,1–1,5% łagodnych guzów krtani, a objawy wzrostu są nieswoiste [2]. Preferowana obecnie metodą leczenia jest endoskopowy wewnątrzkrtaniowy zabieg operacyjny z użyciem konwencjonalnych narzędzi do mikrochirurgii krtani lub z użyciem lasera CO2.[5] Ta druga metoda zyskuje coraz bardziej na znaczeniu. Użyciu lasera CO_2 zmniejsza ryzyko wystąpienia obrzęku pooperacyjnego, infekcji, skraca czas pobytu pacjenta w szpitalu oraz zmniejsza ryzyko nawrotów [5]. Jednakże w przypadku guzów o dużej masie konieczne mogą być zabiegi z dostępu zewnątrzkrtaniowego, takie jak: tyreotomia pośrodkowa, boczna pharyngotomia czy boczna zewnętrzna tyreotomia z usunięciem górnej połowy blaszki chrząstki tarczowatej [6].

W diagnostyce nerwiaka bardzo ważną rolę odgrywają badania obrazowe zarówno tomografia komputerowa jak i rezonans magnetyczny. W przeanalizowanym piśmiennictwie obraz radiologiczny nerwiaka osłonkowego sugeruje łagodny charakter nowotworu. Guzy opisywane są jako dobrze odgraniczone struktury, nienaciekające chrząstek, nie opisuje się limfodenopati, dodatkowo w MR po podaniu środka kontrastowego (gadolinu) obserwuje się wzmocnienie kontrastowe ściany nerwiaka [3]. Laryngoskopia pośrednia potwierdza łagodny charakter guza jako gładkościenną zmianę, z prawidłową ruchomością strun głosowych. Trzeba jednak pamiętać, że definitywne rozpoznanie nerwiaka i innych nowotworów neuroendokrynnych można postawić jedynie na podstawie badania histopatologicznego i immunohistochemicznego. Biopsja aspiracyjna cienkoigłowa (BAC) jest najmniej wartościowym badaniem [8]. Najczęstszą metodą pozyskiwania materiału do badania histopatologicznego pozostaje mikrodirektoskopia z pobraniem wycinka z guza. Następnie po uzyskaniu wyniku patomorfologicznego pacjent jest kwalifikowany do zabiegu operacyjnego. Pomimo to, M. Tulli i wsp.[3] uważają, że po uzyskaniu w badaniach radiologicznych oraz w laryngoskopii pośredniej obrazu przemawiającego za łagodnym charakterem guza najlepszym rozwiązaniem jest jednoczasowa radykalna resekcja guza.

PODSUMOWANIE

Nerwiak osłonkowy jest bardzo rzadkim nowotworem krtani o bardzo dobrym rokowaniu dla pacjenta, małej tendencji do nawrotu [1, 2].

Przeanalizowane piśmiennictwo dotyczące diagnostyki oraz leczenia nerwiaka osłonkowego okolicy krtani sugeruje, że należy dążyć do zabiegu biopsji wycinającej po uzyskaniu radiologicznego i endoskopowego obrazu o cechach nerwiaka. Takie podejście jest jednocześnie diagnostyczne i lecznicze w przypadku tego typu nowotworu, zmniejsza koszty, jak i narażenie pacjenta na kolejne zabiegi operacyjne.

PIŚMIENNICTWO

1. Ramdass AA, Yao M, Ef SN, Bakshi PK. A Rare Case of Vagus Nerve Schwannoma Presenting as a Neck Mass. Am J Case Rep. 2017;18:908-911. doi:10.12659/AJCR.904084.
2. Romak JJ, Neel HB, Ekbom DC. Laryngeal Schwannoma: A Case Presentation and Review of the Mayo Clinic Experience. J Voice. 2017. doi:10.1016/j.jvoice.2015.12.003.
3. Tulli M, Bondi S, Bussi M. Exeresi mediante approccio mini-invasivo di un voluminoso schwannoma laringeo: Un case report. Acta Otorhinolaryngol Ital. 2017. doi:10.14639/0392-100X-1234.
4. Plantet MM, Hagay C, De Maulmont C et al. Laryngeal schwannomas. Eur J Radiol. 1995;21(1):61-66. doi:10.1016/0720-048X(95)00655-A.
5. Kou W, Zhang C, Wei P. Laryngeal schwannoma treated with a CO2laser: A case report. Oncol Lett. 2015;9(3):1467-1469. doi:10.3892/ol.2015.2858.
6. Nardi CEM, Burzichelli AW, Pfuetzenreiter EG, Dedivitis RA. Schwannoma of the arythenoid. Einstein (Sao Paulo). 2013;11(2):224-226. doi:10.1590/S1679-45082013000200015.
7. Kumar V, Abbas AK, Fausto N et al. Robbins and Cotran Pathologic Basis of Disease. 8th edn. Philadelphia, PA: Saunders; 2010.
8. Bień S, Żyłka S. Nowotwory neurogenne głowy i szyi. Otorynolaryngologia 2004;3(1):40-44.

Konflikt interesów:
Autorzy delarują brak konfliktu interesów.

AUTOR KORESPONDUJĄCY

Jacek Czubak
ul. Boiskowa 19/26, 52-126 Wrocław,
tel.: 794297586
e-mail: jacekcz90@gmail.com

Received: 18.02.2019
Accepted: 15.04.2019