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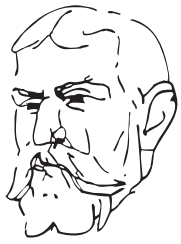

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CEREBRAL PALSY: CLINICAL AND SOCIAL PROBLEMS

MÓZGOWE PORAŻENIE DZIECIĘCE. PROBLEMY KLINICZNE I SPOŁECZNE

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ABSTRACT

Introduction: Cerebral palsy / MPD/is a motor and postural disorder caused by permanent brain damage that occurred at an early stage of development. Cerebral palsy is the most common cause of disability in children.

The aim: To present cerebral palsy as a clinical problem and to outline the importance of physiotherapy in the treatment of cerebral palsy patients.

Materials and methods: The study included 67 children with cerebral palsy (mean age was 9 years) treated and followed up for 6 months at the "Górka" Orthopaedic and Rehabilitation Hospital in Busko Zdrój. The clinical presentation was dominated by manifestations of motor and postural abnormalities resulting from upper motor neuron and corticospinal tract damage. A diagnostic survey was used as the research method. The physiotherapy and rehabilitation used in the patients consisted of kinesiotherapy (usually Bobath/NDT) and physical therapy procedures (magnetic stimulation, laser therapy, LED light therapy). The study used a survey questionnaire that collected information about problems with everyday life and functioning of cerebral palsy patients and opinions about their rehabilitation programme.

Results: Follow-up data were analysed in patient groups, which were created based on the method of ambulation in children with cerebral palsy. The results emphasise the role of physiotherapy in the rehabilitation of cerebral palsy patients. Systematic motor rehabilitation contributed to an improved physical fitness and better everyday functioning. Parents of children walking with aids reported having problems with access to specialist healthcare, which resulted from the fact that they did not live close enough to an appropriate centre. Parents of non-ambulatory patients reported that they lacked financial means and parents of children who were able to walk unassisted complained of long waiting times for rehabilitation.

Conclusions: 1. MPD is a difficult clinical and social problem. 2. Physical improvement procedures is an essential element in the treatment of this group of patients.

KEY WORDS: cerebral palsy, clinical and social problems, physiotherapy

STRESZCZENIE

Wstęp: Mózgowe porażenie dziecięce (MPD) to zespół zaburzeń ruchu i postawy wynikający z trwałego uszkodzenia mózgu we wczesnym stadium rozwoju. Jest to najczęstsza przyczyna niepełnosprawności u dzieci.

Cel pracy: Ukazanie problemu klinicznego, jakim jest MPD oraz znaczenia fizjoterapii w leczeniu tych chorych.

Materiał i metoda: Badaniu poddano 67 dzieci z MPD w wieku średnio 9 lat leczonych i obserwowanych na przestrzeni 6 miesięcy w szpitalu Ortopedyczno-Rehabilitacyjnym Górka w Busku Zdroju. W obrazie klinicznym u chorych dominowały: objawy zaburzeń ruchu i postawy wynikające z uszkodzenia górnego neuronu ruchowego i dróg korowo-rdzeniowych. Zastosowano metodę badawczą, jaką jest sondaż diagnostyczny. W postępowaniu fizykalno-usprawniającym stosowano: kinezyterapie, najczęściej metodę NDT Bobath oraz zabiegi fizykalne: magnetostymulację, laseroterapię, ledoterapię. W pracy wykorzystano kwestionariusz ankiety, który obejmował problemy związane z życiem i funkcjonowaniem badanych oraz ocenę przeprowadzonego programu rehabilitacji.

Wyniki: Dane z obserwacji analizowano w grupach wydzielonych ze względu na sposób poruszania się chorych dzieci. Uzyskane wyniki badań podkreślają rolę fizjoterapii w usprawnianiu osób z MPD. Systematycznie prowadzona rehabilitacja ruchowa przyczyniła się do poprawy kondycji fizycznej oraz lepszego funkcjonowania w życiu codziennym. Problem z dostępem do opieki specjalistycznej zgłaszany przez rodziców dzieci chodzących ze sprzętem, wynikał z braku dostatecznie bliskiej placówki. Rodzice dzieci niechodzących zgłaszali brak środków finansowych, a rodzice dzieci chodzących samodzielnie, długi termin oczekiwania na rehabilitacje.

Wnioski: 1. MPD jest bardzo trudnym problemem klinicznym i społecznym. 2. Postępowanie fizykalno-usprawniające jest podstawowym elementem w leczeniu tej grupy chorych

SŁOWA KLUCZOWE: mózgowe porażenie dziecięce, problemy kliniczne i społeczne, fizjoterapia

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INTRODUCTION

Cerebral palsy (CP) is one of the most frequently diagnosed neurological syndromes in children and also the third most common cause of long-term disability worldwide.

Polish epidemiological data indicate that in the general population of neonates, CP is found in 2-3 cases per 1,000 births. Its incidence reaches 5-10% in children from so-called risk groups.

Table 1. Characteristics of study patients with CP in terms of method of ambulation.

Method of ambulation	n	[%]
Walks unassisted	12	17.91%
Walks with orthopaedic aids	16	23.88%
Non-ambulatory	39	58.21%

Table 2. Characteristics of study patients in terms of sex by patient group.

Sex	Walks unassisted		Walks with orthopaedic aids		Non-ambulatory		Total		Chi-squared test
	n	[%]	n	[%]	n	[%]	n	[%]	
Girl	6	50.00%	7	43.75%	17	43.35%	30	44.78%	p=0.915
Boy	6	50.00%	9	56.25%	22	56.41%	37	55.22%	
No response	0	0.00%	0	0.00%	1	2.56%	1	1.49%	

The most general classification of CP includes three types of the disorder: spastic (hemiplegia, hemiplegia bilateralis, diplegia spastica), extrapyramidal , mixed [1–10].

Damage seen in CP leads to increased tendon reflexes and muscle tone. Hypotonic (flaccid) CP causes reduced muscle tone, which results in difficulty maintaining a normal body posture.

Rehabilitation of CP children is based on appropriate functional diagnostic work-up. Their functional status is assessed with various scores, for instance GMFCS, which is used to classify mobility levels and, consequently, motor limitations.

The process of rehabilitation in CP children is difficult because it requires a multilevel approach taking into account the complexity of both the manifestations and the clinical types of cerebral palsy. Consequently, it is impossible to develop and implement a uniform standard of management since various types of CP and individual cases (due to the individual development of children) are characterised by a different course of the disorder [11–19].

The rehabilitation of CP children also includes physical therapy procedures, such as massage, hydrotherapy (whirlpool massage; aerated, or "pearl", baths), cryotherapy, electrotherapy, and magnetic field therapy. In order to reduce spasticity, CP patients undergo electrical muscle stimulation. Recent years have seen an increasing number of reports on the use of magnetic stimulation and polarised light therapy [20–28].

Nowadays, the rehabilitation of children with CP is mainly focused on the neurodevelopmental approach and the methods by Berta and Karel Bobath or Vaclav Vojta. Another method used in the rehabilitation of CP children is the conductive education method developed by Peto and Hari, which should be used in children from approximately the 4th year of life. Another method used in CP children was described by Veronica Sherbourne (Sherborne developmental movement).

THE AIM

The aim of this study was to present problems encountered in CP children in the context of their physical therapy and the methods used.

MATERIALS AND METHODS

1. The study used the diagnostic survey method. The survey was completed by parents or guardians of children with cerebral palsy before and after treatment.
2. The study was conducted at the Dr Szymon Starkiewicz "Górka" Specialist Orthopaedics and Rehabilitation Hospital in Busko Zdrój in 2017 in a group of 67 children with cerebral palsy (mean age was 9 years), with a follow-up of 6 months. The clinical presentation was dominated by manifestations of motor and postural abnormalities resulting from upper motor neuron and corticospinal tract damage. The data obtained from patients were statistically analysed.
3. Quantitative variables were analysed with a mean, standard deviation, median, and minimum and maximum quartiles. Qualitative variables were analysed by calculating the number and percentage of each value.
4. The values of quantitative variables in three patient groups were compared using analysis of variance (ANOVA).
5. The significance level for the analysis was set at 0.05. The analysis was performed using R 3.3.0.

RESULTS

Results were analysed in groups, with children divided according to the method of ambulation (Table 1).

Table 2 presents the characteristics of study patients in individual patient groups in terms of sex. The p value from a chi-squared test was higher than 0.05, which meant there were no significant differences between the groups.

The characteristics of CP children, divided into three groups, in terms of age can be found in Table 3. Mean age of study patients was 9.05 years (SD=4.68) and ranged between 1 year and 10 months (1.83 years) and 19 years. The median was 8 years.

CP patients were characterised in the three groups in terms of their place of residence; 34.3% of patients lived in villages and 44.75% lived in cities with more than 100,000 residents.

CP types by patient group are characterised in Table 4. The p value from a chi-squared test was less than 0.05, which means that differences between the groups are statistically significant.

Table 3. Characteristics of study patients in terms of age by patient group.

Group	Age of child [years]								p
	N	Mean	SD	Median	Min	Max	Q1	Q3	
Walks unassisted	12	10.04	4.75	9.5	2.5	16	6.75	15	
Walks with orthopaedic aids	16	7.19	3.1	8.5	2	10	4	10	p=0.178
Non-ambulatory	39	9.52	5.07	8	1.83	19	5.5	13.5	
Total	67	9.05	4.68	8	1.83	19	5	13	

Table 4. Characteristics of CP types by patient group.

CP type	Walks unassisted		Walks with orthopaedic aids		Non-ambulatory		Total		Chi-squared test
	n	[%]	n	[%]	n	[%]	n	[%]	
Spastic hemiplegia	6	50.00%	2	12.50%	2	5.13%	10	14.93%	p=0.025
Spastic diplegia	4	33.33%	6	37.50%	19	48.72%	29	43.28%	
Bilateral hemiplegia	1	8.33%	5	31.25%	7	17.95%	13	19.40%	
Ataxic cerebral palsy	1	8.33%	0	0.00%	1	2.56%	2	2.99%	
Extrapyramidal palsy	0	0.00%	1	6.25%	6	15.38%	7	10.45%	
Mixed type	0	0.00%	2	12.50%	4	10.26%	6	8.96%	

Study patients with CP were characterised in terms of comorbidities by patient group. Eye disorders were most common in non-ambulatory patients and least common in children walking with aids.

Speech disorders were most common in non-ambulatory patients and least common in patients able to walk unassisted. Balance problems were most common in children able to walk. The lower the level of independence in mobility, the higher the level of mental impairment.

Table 5 presents the characteristics of study patients in terms of requiring help in activities of daily living by patient group.

CP patients in the three groups were characterised in terms of the age at which they started rehabilitation. The mean age at which study patients started rehabilitation was 4.24 months (SD=6.76; range: 1 to 36 months).

Table 6 presents the type of education of study patients with CP by patient group. Children who walked unassisted or with orthopaedic aids were usually educated in inclusive education environments and non-ambulatory patients received special-needs education.

Table 7 presents the methods used in CP children by patient group: therapeutic massage was most common in children able to walk unassisted and least common in children walking with aids.

Special methods and music therapy were most common in non-ambulatory patients and least common in patients able to walk unassisted.

Hippotherapy was most common in non-ambulatory patients and least common in children walking with aids and able to walk unassisted.

Orthopaedic aids were most common in children walking with orthopaedic aids and least common in children able to walk unassisted.

Special methods of rehabilitation used in CP patients by patient group are presented in Table 8. Bobath/NDT was most common in children walking with orthopaedic aids and least common in patients walking unassisted.

As far as the number of special methods of rehabilitation used in CP patients in the three groups was considered, children walking with aids used a significantly larger number of special methods than children able to walk unassisted.

Physical therapy procedures used in CP children by patient group are presented in Table 9.

The number of special methods used in CP children is presented in Table 10.

The frequency of rehabilitation procedures in children with CP is presented in Table 11.

The parents' assessment of the efficacy of rehabilitation can be found in Table 12. The chi-squared test p value is lower than 0.05, which means that differences between the groups are statistically significant. The higher the level of independence in a child, the better the opinion about the efficacy of their rehabilitation.

DISCUSSION

Cerebral palsy is non-progressive (the brain damage is permanent and does not progress during the patient's life), but its manifestations become more visible with time. The intellectual level of patients with CP is usually similar to that of the general population and their mean life expectancy is nowadays the same as in the general population. Anderson and Mattsson [22] conducted research on a group of 221 CP patients aged 20 to 58 years and found

Table 5. Characteristics of CP patients in terms of requiring help during activities of daily living by patient group.

Requires help in activities of daily living	Walks unassisted		Walks with orthopaedic aids		Non-ambulatory		Total		Chi-squared test
	n	[%]	n	[%]	n	[%]	n	[%]	
Yes	5	41.67%	15	93.75%	36	92.31%	56	83.58%	p<0.001
No	7	58.33%	1	6.25%	3	7.69%	11	16.42%	

Table 6. Type of education in study patients by patient group

Type of education	Walks unassisted		Walks with orthopaedic aids		Non-ambulatory		Total		Chi-squared test
	n	[%]	n	[%]	n	[%]	n	[%]	
Home education	1	8.33%	1	6.25%	10	25.64%	12	17.91%	p=0.001
Inclusive education	6	50.00%	12	75.00%	4	10.26%	22	32.84%	
Special-needs education	4	33.33%	0	0.00%	17	43.59%	21	31.34%	
Child not receiving education	1	8.33%	3	18.75%	7	17.95%	11	16.42%	
No response	0	0.00%	0	0.00%	1	2.56%	1	1.49%	

that 39% of study patients were able to walk without orthopaedic aids at home and outside of the house, 27% never learned to walk, and a third complained of gait worsening, increasing spasticity, and balance problems.

CP requires appropriate diagnosis and treatment; the disorder is accompanied by multiple specific dysfunctions, which directly affect the emotional and social functioning of patients [23–28].

The process of rehabilitation in CP children is difficult and requires a comprehensive approach that takes into account the complexity of manifestations and clinical types of CP. It is usually impossible to develop and implement a uniform standard of management since the course of CP is usually varied, which is associated with the individual development of children. It is necessary to use a type of management that allows for controlling the compensating mechanisms of the body as much as possible and results in the most desired therapeutic effect [27, 28].

It is very important for parents of children with CP to work closely with physiotherapists during the rehabilitation process. The rehabilitation of children with cerebral palsy is based on kinesiotherapy and physical therapy procedures, which complement and support the functions of the body to help prepare for exercise or improve symptoms that hinder rehabilitation. Physical therapy procedures such as massage, hydrotherapy (including whirlpool massage and aerated baths), cryotherapy, electrotherapy, and magnetic field therapy play an important role in the rehabilitation of children with cerebral palsy [25–28].

The rehabilitation process of CP children should be based on neurophysiological mechanisms and should be adjusted to the maturity of the central nervous system. The perception of external stimuli helps develop the cognitive abilities of children and increases the activity of brain maturity processes. Neuroplasticity allows children to remember normal motor patterns and inhibits pathological patterns. New stimuli in the form of variable magnetic fields accelerate appropriate neuroplasticity processes and help patients repeat motor patterns faster, while decreasing muscle tone [23].

Studies show that magnetic stimulation has beneficial effects on spasticity in children with CP and helps increase the level of psychomotor abilities, as assessed with appropriate scores and diagnostic tools [23].

The present study attempted to assess problems encountered in physical therapy performed in children with cerebral palsy. The study group consisted of 67 children diagnosed with CP. Of the study patients, 12 children were able to walk unassisted, 16 children walked using orthopaedic aids, and 39 children were non-ambulatory. Mean age of study patients was 9.05 years (range: 1 year 10 months [1.83 years] to 19 years). Median was 8 years; patients were usually aged 5 to 13 years.

Children with CP who were able to walk unassisted were diagnosed with cerebral palsy in the neonatal period based on the Apgar score or in the 2nd year of life; they were usually diagnosed with spastic hemiplegia or, less frequently, spastic diplegia. Children who used orthopaedic aids were diagnosed with CP in the 1st or 2nd year of life; they were usually diagnosed with spastic diplegia and bilateral hemiplegia. In the case of children unable to walk, CP was diagnosed as early as in the neonatal period or in the 1st year of life; spastic diplegia was most common.

As far as concomitant diseases in the study group were concerned, eye disorders were most common in non-ambulatory children and rare in children walking with the use of orthopaedic aids. Speech disorders were most common in non-ambulatory children and less common in children able to walk unassisted. Coordination problems were most

Table 7. Therapeutic methods used in CP patients by patient group.

Therapeutic method	Walks unassisted		Walks with orthopaedic aids		Non-ambulatory		Total		Chi-squared test
	n	[%] *	n	[%] *	n	[%] *	n	[%] *	
Pharmacotherapy	6	50.00%	1	6.25%	19	48.72%	26	38.81%	p=0.009
Kinesiotherapy	10	83.33%	11	68.75%	31	79.49%	52	77.61%	p=0.598
Therapeutic massage	10	83.33%	4	25.00%	22	56.41%	36	53.73%	p=0.008
Hydrotherapy	4	33.33%	4	25.00%	12	30.77%	20	29.85%	p=0.876
Water exercise	8	66.67%	5	31.25%	15	38.46%	28	41.79%	p=0.138
Dog-assisted therapy	4	33.33%	0	0.00%	23	58.97%	27	40.30%	p<0.001
Special methods	0	0.00%	6	37.50%	23	58.97%	29	43.28%	p=0.001
Hippotherapy	3	25.00%	4	25.00%	25	64.10%	32	47.76%	p=0.007
Music therapy	1	8.33%	5	31.25%	19	48.72%	25	37.31%	p=0.035
Physical therapy methods	1	8.33%	5	31.25%	7	17.95%	13	19.40%	p=0.297
Orthopaedic aids	4	33.33%	16	100.00%	30	76.92%	50	74.63%	p<0.001
Reflexotherapy	0	0.00%	1	6.25%	4	10.26%	5	7.46%	p=0.486
Kinesiotaping	0	0.00%	0	0.00%	2	5.13%	2	2.99%	p=0.477
Speech therapy	0	0.00%	0	0.00%	1	2.56%	1	1.49%	p=0.695
SI	0	0.00%	0	0.00%	1	2.56%	1	1.49%	p=0.695

* Response percentages do not add up to 100% since it was a multiple choice question

Table 8. Special methods of rehabilitation used in CP patients by patient group

Special methods	Walks unassisted		Walks with orthopaedic aids		Non-ambulatory		Total		Chi-squared test
	n	[%] *	n	[%] *	n	[%] *	n	[%] *	
Vojta method	8	66.67%	14	87.50%	26	66.67%	48	71.64%	p=0.272
Bobath/NDT	4	33.33%	15	93.75%	26	66.67%	45	67.16%	p=0.003
Peto method	0	0.00%	0	0.00%	4	10.26%	4	5.97%	p=0.217
Sensory integration (SI)	4	33.33%	11	68.75%	21	53.85%	36	53.73%	p=0.177

* Response percentages do not add up to 100% since it was a multiple choice question

common in children using orthopaedic aids and less common in children able to walk unassisted.

The study showed that the lower the level of gait independence, the higher the level of mental impairment. Difficulties with sitting were found only in non-ambulatory children; however, it was also found that children able to walk unassisted required the least amount of support in the activities of daily living.

As for the type of education in CP children, patients able to walk unassisted or with the use of orthopaedic aids usually received inclusive education and non-ambulatory children received special education. All study patients were usually given specialist care. The help of teachers and physiotherapists was most common in the group of non-ambulatory children and rare among children able to walk unassisted. The number of patients receiving care from physiotherapists was the highest among children walking with orthopaedic aids and the lowest among children able to walk unassisted. CP children from the three groups were treated with various methods. Dog-assisted therapy was most common in non-ambulatory children and least common in children walking with orthopaedic aids, whereas special methods and music therapy were most common in non-ambulatory patients and least common in children able to walk unassisted. The last group of methods, i.e. orthopaedic aids, was most common among children walking with orthopaedic aids and rare in children able to walk unassisted.

Bobath/NDT was most common in children walking with orthopaedic aids and less common in children able to walk unassisted.

Of the physical therapy procedures used in the study group, magnetic stimulation was the most commonly used method in children walking with aids and was less common in non-ambulatory children.

Patients from the study group also underwent other physical therapy methods in the form of laser therapy, LED light therapy, and vibration mats (mainly children able to walk unassisted).

Table 9. Physical therapy procedures used in CP patients by patient group.

Physical therapy procedures	Walks unassisted		Walks with orthopaedic aids		Non-ambulatory		Total		Chi-squared test
	n	[%] *	n	[%] *	n	[%] *	n	[%] *	
Electrical muscle stimulation	3	25.00%	4	25.00%	9	23.08%	16	23.88%	p=0.984
Magnetic stimulation	4	33.33%	8	50.00%	5	12.82%	17	25.37%	p=0.012
Warm compresses	3	25.00%	3	18.75%	16	41.03%	22	32.84%	p=0.228
Whirlpool massage	8	66.67%	8	50.00%	20	51.28%	36	53.73%	p=0.609
Infrared radiation	6	50.00%	4	25.00%	17	43.59%	27	40.30%	p=0.333
Local cryostimulatio	0	0.00%	0	0.00%	1	2.56%	1	1.49%	p=0.695
Visible polarised light	0	0.00%	0	0.00%	2	5.13%	2	2.99%	p=0.477
Laser therapy	3	25.00%	0	0.00%	0	0.00%	3	4.48%	p=0.001
LED light therapy	3	25.00%	0	0.00%	0	0.00%	3	4.48%	p=0.001
Vibration mat	3	25.00%	0	0.00%	0	0.00%	3	4.48%	p=0.001
Not performed	5	41.67%	4	25.00%	10	25.64%	19	28.36%	p=0.528

* Response percentages do not add up to 100% since it was a multiple choice question

Table 10. Number of special methods of rehabilitation used in children with CP by patient group.

Group	No. of physical therapy procedures								p
	N	Mean	SD	Mediana	Min	Max	Q1	Q3	
Walks unassisted	12	3.17	2.12	3.5	1	6	1	4.5	
Walks with orthopaedic aids	16	1.94	1.65	1.5	0	5	1	2	p=0.081
Non-ambulatory	39	2.05	1.36	2	0	6	1	3	

Table 11. Frequency of rehabilitation procedures in CP children by patient group.

Frequency of rehabilitation procedures in children	Walks unassisted		Walks with orthopaedic aids		Non-ambulatory		Total		Chi-squared test
	n	[%] *	n	[%] *	n	[%] *	n	[%] *	
Every day, by specialists	0	0.00%	0	0.00%	10	25.64%	10	14.93%	p=0.015
Once a week, by parents	4	33.33%	0	0.00%	0	0.00%	4	5.97%	p<0.001
Several (2-3) times a week, by specialists	3	25.00%	12	75.00%	18	46.15%	33	49.25%	p=0.027
Several (2-3) times a week, by parents	6	50.00%	10	62.50%	25	64.10%	41	61.19%	p=0.676
Once a week, by specialists	4	33.33%	4	25.00%	7	17.95%	15	22.39%	p=0.514

* Response percentages do not add up to 100% since it was a multiple choice question

Table 12. Rehabilitation efficacy assessed by parents.

Assessment of rehabilitation efficacy	Walks unassisted		Walks with orthopaedic aids		Non-ambulatory		Total		Chi-squared test
	n	[%]	n	[%]	n	[%]	n	[%]	
Very good, child making good progress	8	66.67%	7	43.75%	8	20.51%	23	34.33%	p=0.009
Good, rehabilitation is very long, but there is visible progress	3	25.00%	9	56.25%	17	43.59%	29	43.28%	
Satisfactory, no progress, condition not worsening	0	0.00%	0	0.00%	11	28.21%	11	16.42%	
Poor, no progress, condition is worsening	0	0.00%	0	0.00%	0	0.00%	0	0.00%	
No response	1	8.33%	0	0.00%	3	7.69%	4	5.97%	

The frequency of rehabilitation procedures in children with CP depended mostly on the children's guardians and on their access to highly specialised medical teams. The study also showed a problem with ensuring that children with CP had access to appropriate rehabilitation, which was mainly caused by the fact that the children did not live close enough to an appropriate centre, the lack of financial means for rehabilitation, or the lack of available appointment slots at specialist centres. The problem of not living near an appropriate centre was usually reported by parents of children walking with aids and was rare among parents of children walking unassisted. The lack of financial means for appropriate rehabilitation was a problem mainly for parents of non-ambulatory patients, while parents of children able to walk unassisted usually complained of the lack of available appointment slots for rehabilitation (waiting time).

To sum up, rehabilitation with neurodevelopmental methods in children with central nervous system damage is increasingly often supplemented with additional methods, including physical therapy methods such as light therapy, cryotherapy, and magnetic stimulation. The latter is a very valuable method supporting rehabilitation in children with cerebral palsy.

CONCLUSIONS

1. MPD is a difficult clinical and social problem.
2. Physical improvement procedures is an essential element in the treatment of this group of patients.

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Conflicts of interest
The Authors declare no conflict of interest.

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CLINICAL AND MORPHOLOGICAL CORRELATIONS AND HISTOPATHOLOGY OF JOINT DAMAGE IN PATIENTS WITH DIFFUSE-TYPE TENOSYNOVIAL GIANT CELL TUMOR

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ABSTRACT

Introduction: Tenosynovial giant cell tumor (TSGCT) (synonym – pigmented villonodular synovitis) – is a rare benign proliferative lesion of the synovial sheath, localized in the joint capsule, bursa or tendon sheath and characterized by locally destructive growth. Depending on the prevalence within the joint elements, the presence of a capsule around the tumor, histophotographic features of cell structure and clinical behavior TSGCT can be divided to localized or diffuse type.

The aim of the study was researching of histopathological properties of diffuse-type TSGCT, determine the parameters its morphological indicators and to find out the correlation between these morphological and clinical parameters.

Materials and methods: The research material was used biopsy (resect) of pathological lesions from 50 patients who were diagnosed and histologically verified diffuse-type TSGCT. Microscopic examinations of the stained sections and their photo archiving were carried out with use of a Olympus-CX 41 light optical microscope. Group measurable parameters (mean values and Pearson tetrachoric index (association coefficient) were calculated in groups of comparison for morphological and clinical indices of TSGCT. The mean values were compared by Student's test, P value of ≤0.1 was considered statistically significant.

Results: Correlation analysis of indicators that accounted for the pairs of cases «clinic – morphology» revealed the relationships, that had the highest parameters of the association coefficient between such indicators: «presence of villous growths» - «severity of hemosiderosis» (if hypertrophied synovial villi available, with vascular injection and pronounced proliferation of synovial cells, there is also a significant accumulation of hemosiderin pigment); «presence of villous growths» - «type of predominant cellular proliferates» (if cells of TSGCT diffuse type consists of monotonous sheets of stromal cells, with uniform, oval to reniform nuclei, the proliferation of villi in synovial layer is non-distinctive); «presence of nodes» - «kind of stroma» (if nodes predominate, their histological structure is mainly represented by polymorphic clusters of synovitis cells in the form of cells, strands, chains, solid formations, among immature connective tissue with low hyalinosis); «cell size (area, cm^2)» - «severity of haemosiderosis» and «cell size (area, cm^2)» - «the number of multinucleated giant cells» (there is a pronounced deposition of pigment and accumulation of osteoclast-like multinucleated giant cells type, although usually their number is relatively small compared to the localized type of TSGCT).

Conclusions: Morphological parameters, that we have identified, characterize pathological changes in the tissues of TSGCT; careful analysis of the frequency of their occurrence in the different comparison groups made it possible to establish intergroup differences and correlations between individual indicators, which were previously unknown or not obvious. Our study was determine to analyze of incidence rates and correlation relationships, revealed some previously unknown differences and dependencies that are important for understanding the pathogenesis, improvement of diagnosis and prognosis of diffuse-type TSGCT.

KEY WORDS: tenosynovial giant cell tumor of diffuse type, histologic structure, correlative analysis

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INTRODUCTION

Tenosynovial giant cell tumor (TSGCT) (synonym – pigmented villonodular synovitis) is a rare benign proliferative lesion of the synovial sheath, localized in the joint capsule, bursa or tendon sheath and characterized by locally destructive growth. According to Myers data (1980) the annual global incidence of TSGCT was 1.8 cases per 1 million populations [1], According to Murphey data (2008) the annual global incidence of TSGCT was 9.2 cases per 1 million populations [2]. Depending on the prevalence within the joint elements, the presence of a capsule around the tumor, histotopographic features of cell structure and clinical behavior TSGCT can be divided to localized or diffuse type. Each form of TSGCT is characterized by specific clinical, visual, macroscopic and histological characteristics, which altogether determine the approach to differential diagnosis and therapeutic strategy that can be applied. As usual, diffuse type of TSGCT is characterized by more aggressive clinical behavior than cases of localized type, has a pronounced tendency for recurrence (from 8% to 56%) after surgical removal, and in rare cases has the potential for malignant transformation [3, 4]. Sharma and Cheng identified 2 main factors that associated with a higher recurrence rate - a diffuse type of the tumor and arthroscopic partial synovectomy in cases of diffuse TSGCT [5].

Many theories have been put forward to explain the pathogenetic mechanisms of synovial cell proliferation in cases of this tumor, but its etiology remains controversial. Etiologic factors that may act as triggers for growth of this neoplasm

are history of trauma with the presence of hemarthrosis, the focus of chronic inflammation in the joint capsule (hyperplastic growths as a consequence of chronic antigenic stimulation), pathology of the cellular and humoral parts of the immune system, local lipid metabolism disorders, etc. [6]. TSGCT for a long time was considered as an inflammatory response of unknown etiology, but in-depth cytogenetic and molecular studies have provided evidence to support the neoplastic nature of this lesion – monoclonal origin (DNA replication from a precursor stem cell), centrifugal nature of the tumor growth (proliferation of cells from center to the periphery) with the possibility of locally aggressive growth into surrounding tissues [5].

The main symptoms in cases of TSGCT is quite nonspecific and includes pain of varying severity, edema of the joint, enlargement of joint volume, blockage of movements in the joint, and development of contracture, if neoplasm growth without any therapeutic effect.

The most often localization for diffuse type of TSGCT is knee, in this case lesion manifests with the signs and consequences of synovial cells proliferation, while the development of TSGCT in hip or ankle joint make an appearance by degenerative symptoms, as a manifestation of secondary deforming arthrosis [1, 7]. The diffuse-type TSGCT tends to invasion up growth of tumor masses beyond the capsule and erosion of adjacent articular cartilage and subchondral bone [8]. Erosion is caused by the action of metalloproteinases, which play an important role in stimulating osteoclastic bone resorption. Expression of the metalloproteinases is caused by local overproduction of cytokines such as TNFα, IL-1, IL-6 [1, 2, 9].

Diffuse forms of TSGCT usually have intra-articular localization, visualized on MR-images like a form of a soft tissue of non-uniform structure with concomitant effusion in the joint cavity [10]. One of the characteristic symptoms on the MRI pattern is the so-called "blooming effect", which is ensured by the presence of hemosiderin, which causes a low signal intensity. As hemosiderin is a magnetic material, as a result of its accumulation in TSGCT's tissue spotted or wide areas of low signal within the synovial membrane are observed [9, 11, 12].

Histologically, a typical TSGCT cell consists of a predominant single-nucleus component, which contains small histiocytic cells and larger, rounded or oval synovial cells, with dense eosinophilic cytoplasm. Background mononuclear-macrophage inflammatory infiltrate is combined with fields of xanthoma cells, relatively small number of osteoclast-like giant cells, and siderophages [11]. All types of TSGCT (both localized and diffuse) usually contain pigment, although the degree of hemosiderin deposition is more noticeable in the case of diffuse intra-articular tumor growth [4].

THE AIM

The purpose was to study the histopathological properties of diffuse-type TSGCT, determine the parameters of morphological indicators of TSGCT cells and to find out the correlation between these morphological and clinical parameters.

MATERIALS AND METHODS

The research material was used biopsy (resect) of pathological lesions from 50 patients who were diagnosed and histologically verified diffuse-type TSGCT. Pathologically altered tissues were fixed, cut into pieces with preservation of it's topography, histologically prepared and sections were made. For histological examination were selected pieces of pathological tissue in the joint capsule, which underwent routine histological processing (tissue samples were fixed in 10% solution of neutral buffered formalin. Serial histological sections were prepared according to standard methods and stained with haematoxylin and eosin). Microscopic examinations of the stained sections and their photo archiving were carried out with use of a Olympus-CX 41 light optical microscope. Graduations of explicitness of morphological indicators were evaluated according to the visual-analogue scale from low to high with increasing 100x. Statistical analysis was performed using the program "Statistica 6.0". Group measurable parameters (mean values and Pearson tetrachoric index (association coefficient) were calculated in groups of comparison for morphological and clinical indices of TSGCT. The mean values were compared by Student's test, p value of ≤0.1 was considered statistically significant. [13].

In clinical, sonographic, MRI and radiological studies of diffuse-type TSGCT cells, a number of its characteristics were considered, that is: age and sex of patients, localization, hyperplastic growths in the joint, trauma history or episodes of overwork, size, macroscopic figuration, signs of invasive growth in the surrounding tissues. After careful histological examination, the morphological indicators were highlighted and quantified. This signs define the grade of soft tissue damage and how common they are (table 1). A correlation analysis was performed to determine the tetrachoric index of association (association coefficient) between clinical and morphological indicators, determined the parameters and the absolute value of the communication index, its sign and the degree of probability (table 2).

RESULTS

Diffuse type of TSGCT usually affected large joints (according to our data, more than half of cases were observed in the knee). The initial symptoms, noted by the majority of patients are pain and swelling of the affected joint, which are eventually accompanied by limitation of movements and inability to load the affected limb. The initial sign of cell growth is often joint swelling, which is not accompanied by pain, local hyperthermia sometimes observed. As a rule, the intensity of these symptoms increases gradually and leads to contracture.

MRI-study describes diffuse-type of TSGCT as a hypo-intensive tumor in the joint capsule, round or oval shape, with heterogeneous structure, sometimes clearly demarcated (in areas of nodular growths in the joint cavity), which are usually associated with exudative synovitis (fig. 1). A common visual feature of diffuse-type TSGCT is the presence of multiple hypo-intensive inclusions in the joint capsule (areas of hemosiderin deposition) (fig. 2).

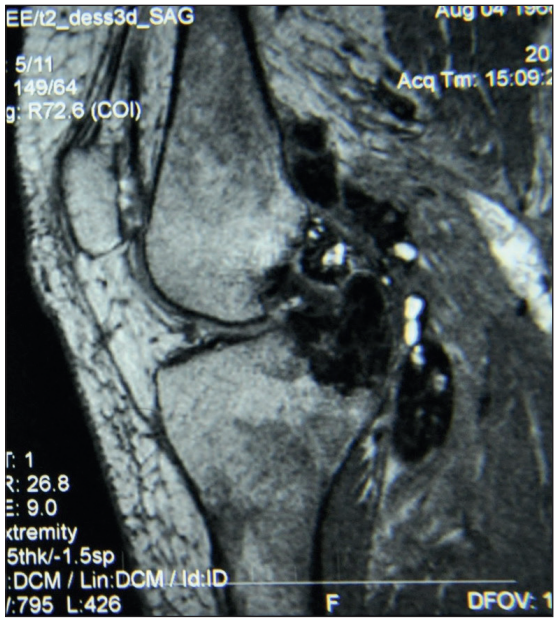

Fig. 1. MRI- anatomy of tenosynovial giant cell tumor, diffuse type, affecting knee joint. It looks like rounded shape neoplasm which extends within the joint capsule and has significant signs of invasion into articular surfaces.

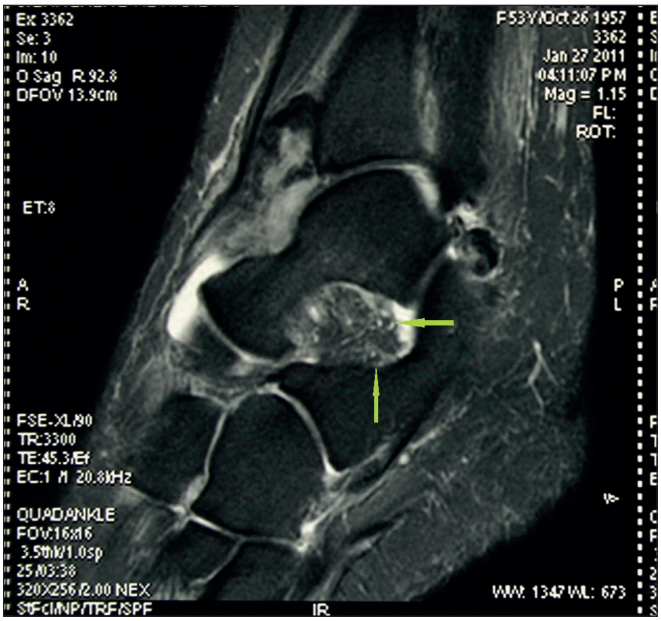

Fig. 2. MRI- anatomy of tenosynovial giant cell tumor, diffuse type, affecting ankle. Tumor tissue has a heterogeneous structure and contains numerous hypointensive inclusions (marked by arrows) – hemosiderin deposits.

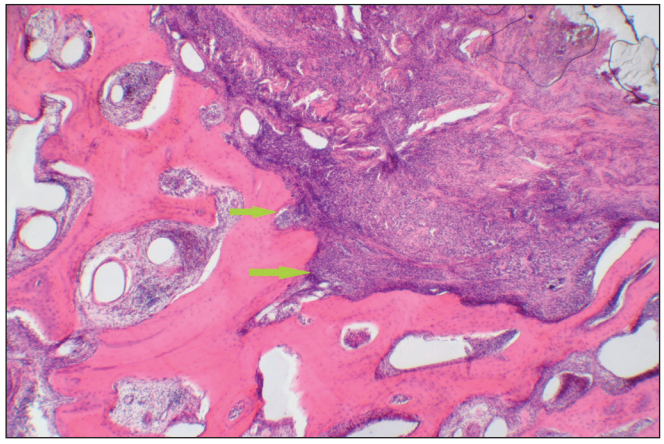

Fig. 3. Infiltrate growth of pathological tissue into subchondral bone tissue and sites of the articular surface's osteodestruction. Haematoxylin and eosin staining, × 30.

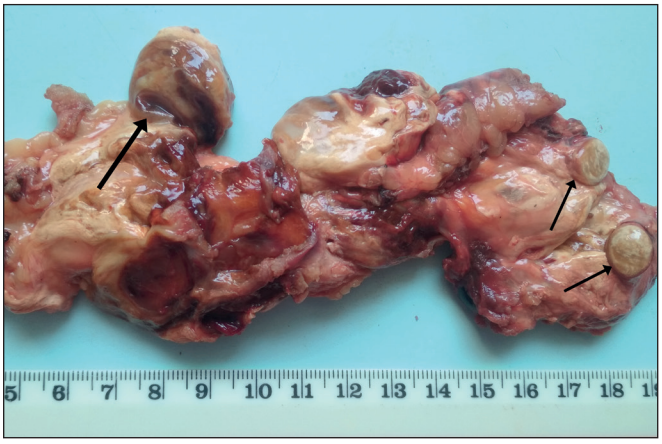

Fig. 4. Macroscopic view of tenosynovial giant cell tumor, diffuse type with plots of the nodular tissue growth (marked by arrows).

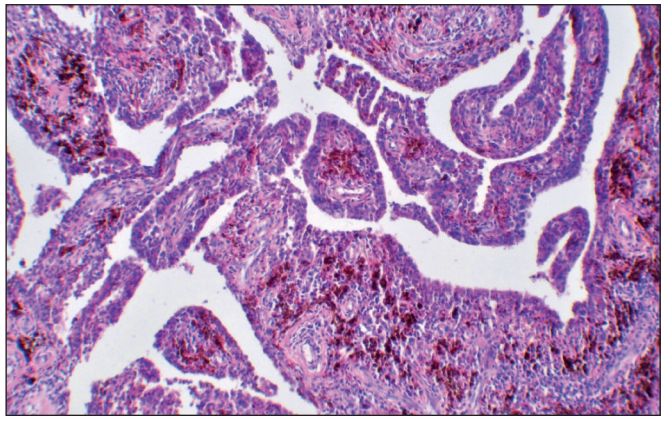

Fig. 5. Hypertrophic villous growths and clusters of siderophages under the synovial layer of joint capsule. Haematoxylin and eosin staining, × 30.

Over time proliferation of the tumor advance and degenerative damage of the articular cartilage combined with the focuses of chondromalacia. Imaging data contains information about thinning and irregularity of the cartilage, covering the femural and tibial condyles, marginal osteophytes, signs of subchondral sclerosis of spongiosis. Early radiological manifestations include synovial swelling, exudation in the joint cavity; as the tumor nodes grow, destruction of the articular surfaces leads to juxta-articular and subchondral erosion and cystic bone remodeling [14]. Local destruction of articular cartilage and spongiosis of the condyles provided by infiltrative growth of pathological tissue leads to expansion of synovial cells in the intertrabeculae spaces and depravation of degenerative changes in the articular surfaces (fig. 3).

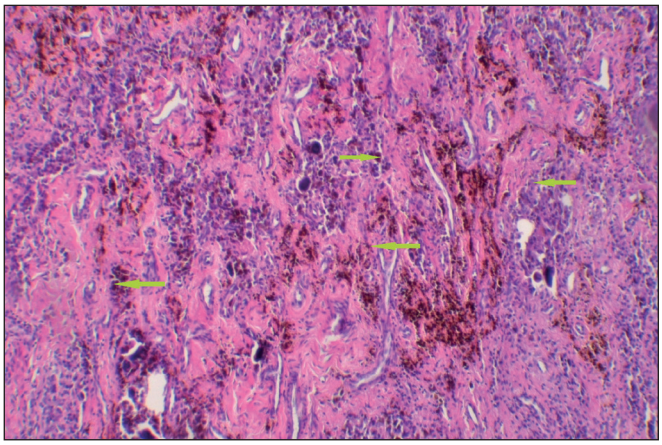

Fig. 6. Mature hyalinized fibrous stroma (marked by arrows) mixed with hypercellular thin-fiber connective tissue. Haematoxylin and eosin staining, ×75.

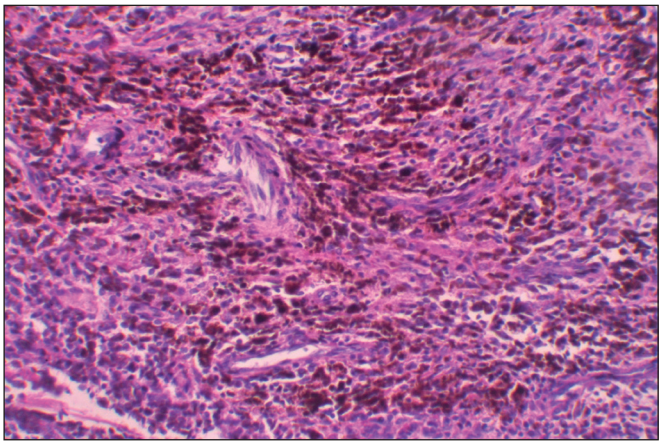

Fig. 7. Diffuse accumulation of hemosiderin pigment among tumor tissue. Haematoxylin and eosin staining, × 150.

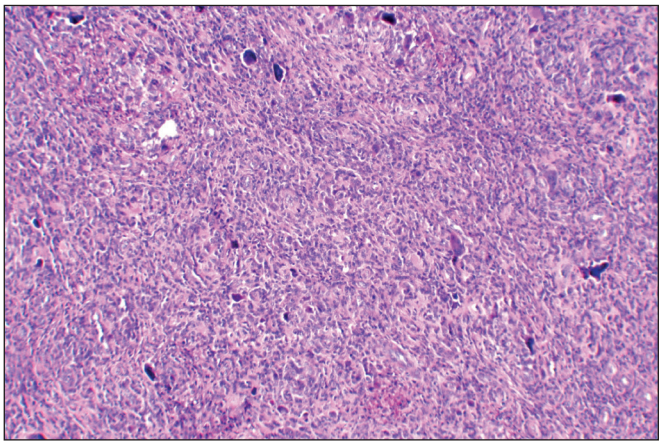

Fig. 8. The cell population is polymorphous comprising large histiocytoid cells with abundant eosinophilic cytoplasm and eccentric vesicular nuclei. Haematoxylin and eosin staining, × 30.

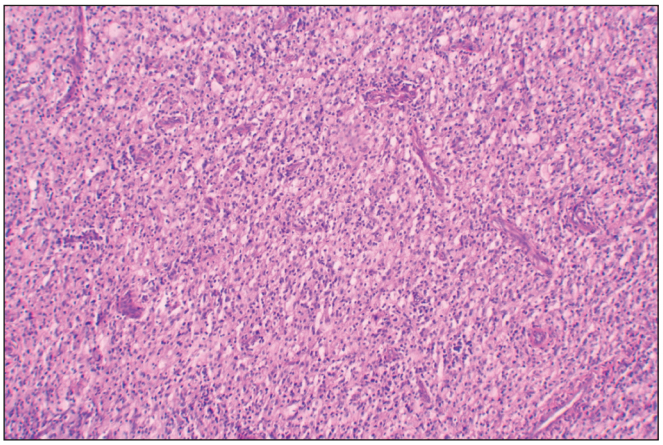

Fig. 9. Proliferation of synovial-like cells in conjunction with mononuclear inflammatory infiltrates and sheets of xanthomas cells. Haematoxylin and eosin staining, × 75.

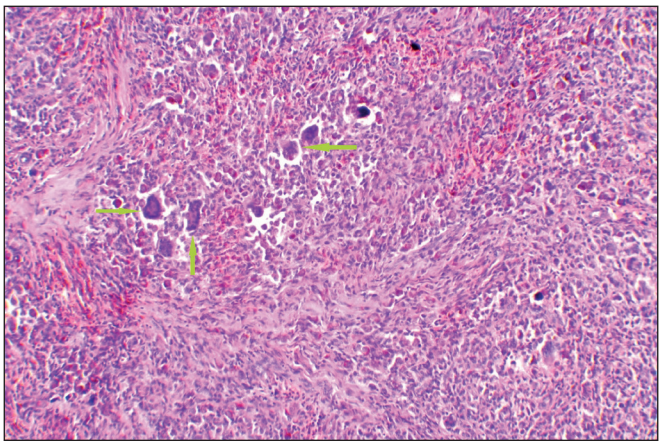

Fig. 10. In case of the diffuse type of tenosynovial giant cell tumor, multinucleated giant cells (marked by arrows) are less widespread at the nodes of the tumor and not as equally distributed as it is observed in localized form. Haematoxylin and eosin staining, ×75.

A macroscopic view of a diffuse-type TSGCT characterized by marked hypertrophy of the synovial cover and large nodes of pathological tissue (fig. 4) or hypertrophy synovial villis.

The tumor tissue has a rust-red or yellow-brown color. Exploring of biopsy specimens from patients with TSGCT shows numerous nodular or villous outgrowths on the internal surface of the articular capsule (fig. 5).

In the villus, its own synovial plate, even in the fibrous layer of the joint capsule, localized hypercellular fields with moderately pronounced signs of infiltrative growth. The severity of fibrosis is variable in the tumor tissue (fig. 6); often happens regions with brown pigment (hemosiderin) (fig. 7).

Proliferative foci are built like nests and solid clusters of synovial cells (fig. 8), among them occurs large cells – epithelioid synovial cells, but without signs of cellular atypism.

This proliferative areas contains mitoses (up to 10 in 10 n / s 400 x); also exists fields of mononuclear cells, macrophages, extensive areas of xanthomas infiltration (fig. 9), multinucleated osteoclast-like giant cells. Giant cells are less congenial in the structure of diffuse-type TSGCT compared with localized type, but between other tumor cells can also occur in the background of microhemorrhages, accumulation of siderocytes and foamy cells (fig. 10).

Correlation analysis of indicators that accounted for the pairs of cases "clinic - morphology" (table 2) revealed

Table 1. Frequency of incidence of cases with different severity of clinical and morphological parameters in patients with tenosynovial giant cell tumor (TSGCT) diffuse type

Clinical indicators	Grades of expression	Number of cases	Frequency in research material, %
	Clinical indicators		
Sex	Male	19	40
	Female	29	60
	All cases are taken into account	48	100,00
Localization (affected joint)	Ankle	4	8
	Wrist	6	12
	Knee	29	58
	Hip	4	8
	Foot	7	14
	All cases are taken into account	50	100,00
Age	Middle age	37,8	
	Median age	35	
	All cases are taken into account	50	100,00
History of trauma	The trauma that preceded the onset of symptoms	23	56
	The injury is absent	18	44
	All cases are taken into account	41	100,00
Prescription of symptoms of joint damage	Average, months	45	
	All cases are taken into account	37	100,00
Invasive growth in surrounding tissue	There are signs of invasive growth	26	65
	No	14	35
	All cases are taken into account	40	100,00
Pain	Present	36	88
	No	5	12
	All cases are taken into account	41	100,00
Swelling	Present	26	64
	No	15	36
	All cases are taken into account	41	100,00
Restrictions of joint movements, stiffness	Present	31	76
	No	10	24
	All cases are taken into account	41	100,00
Local joint hyperthermia	Present	10	24
	No	31	76
	All cases are taken into account	41	100,00
Contracture of the joint	Present	25	63
	No	15	37
	All cases are taken into account	40	100,00
The size of the tumor	Average (area in cm^2)	52	
	All cases are taken into account	34	100,00
The presence of villous growths	Present	8	20
	No	31	80
	All cases are taken into account	39	100,00
The presence of nodular formations	Present	34	87
	No	5	13
	All cases are taken into account	39	100,00

Morphological indicators			
Morphological indicators	Grades of expression	Number of cases	Frequency in research material, %
Intensity (severity) of mononuclear-macrophage inflammatory infiltration	Low degree: Poorly expressed, single cells, loose	19	38
	Medium: Moderate, xanthocellular infiltration is poor or absent	8	16
	High Grade: Well expressed, medium or high density with significant xanthocellular infiltrates	23	46
	All cases are taken into account	50	100,00
The presence of multinucleated osteoclast-like giant cells	Low degree: None	7	14
	Medium: Minor: Occurs in only a few p / s. small increase.	29	58
	High degree: Occurs regularly, at many loci, ie at each p / s. small increase	14	28
	All cases are taken into account	50	100,00
Prevailing cellular proliferate composition	Low grade: Focal synovitis proliferates	10	20
	Medium: Solid synovitis proliferates with the formation of slit-like histostructures	20	40
	High grade: Diffuse solid proliferates of fibroblasts and synovial cells	20	40
	All cases are taken into account	50	100,00
Severity of haemosiderosis	Low grade: Hemosiderin accumulations are poorly expressed, rare, small	27	54
	High degree: Occurs in many cells, forming clusters of granules and siderocytes	23	46
	All cases are taken into account	50	100,00
Kind of stroma	Hyalinized fibrous stroma predominates	19	38
	The ratio of hypercellular thin-fiber and hyalinized stroma is compared	15	30
	Hypercellular fibroblastic proliferates, fibrous tissue, thin fibrous, hyalinosis is poorly expressed or absent	16	32
	All cases are taken into account	50	100,00

the relationships that had the highest parameters of the association coefficient between such indicators:

- «Presence of villous growths» - «severity of hemosiderosis» - dependence is positive, weak, significant with probability of error p<0,1. It means that if hypertrophied synovial villi available, with vascular injection and pronounced proliferation of synovial cells, there is also a significant accumulation of hemosiderin pigment.
- «Presence of villous growths» - «Type of predominant cellular proliferates» - dependence is negative, weak, significant with probability of error p<0,1. It means that if cells of TSGCT diffuse type consists of monotonous sheets of stromal cells, with uniform, oval to reniform nuclei, the proliferation of villi in synovial layer is not characteristic, and the tumor growth in the joint is represented by large monomorphic fields of cellular infiltration formed by synovitis.
- «Presence of nodes» - «Kind of stroma» - dependence is positive, weak, significant with probability of error p<0,1. It means that if nodes predominate, their histological structure is mainly represented by polymorphic clusters of synovitis cells in the form of cells, strands, chains, solid formations, among immature connective tissue with low hyalinosis.
- «Cell size (area, cm^2)» - «Severity of haemosiderosis» and «Cell size (area, cm^2)» - «The number of multinucleated giant cells» - dependence is positive, weak, and significant with probability of error p <0,05. It means that there is a pronounced deposition of pigment and accumulation of osteoclast-like multinucleated giant cells type, although usually their number is relatively small compared to the localized type of TSGCT. In some cells hemosiderin forms a fine dusty brown staining of the cytoplasm, in others, the cytoplasm looks completely filled with large brown granules.

Table 2. Correlation dependence between clinical and morphological indices of histological structure in tenosynovial giant cell tumor, diffuse type

Clinical indicators	Morphological indicators	Pearson's tetrachoric index (association coefficient) and the probability of its parameter			
		n, the number of cases taken into account with the values of both indicators	r_a	$вt_ф$	Probability assessment r_a by k=n-1 by Student's test
The presence of villous growths	Severity of haemosiderosis	39	+ 0,267	1,731	p<0,1
The presence of villous growths	Prevailing cellular proliferate composition	39	- 0,259	1,673	p~0,1
The presence of nodular formations	Kind of stroma	39	+ 0,287	1,871	p<0,1
The size of the tumor	Severity of haemosiderosis	33	+ 0,394	2,463	p<0,02
The size of the tumor	The presence of multinucleated osteoclast-like giant cells	33	+ 0,335	2,040	p=0,05

The correlation relationships of all other pairs of clinic-morphology indicators were found to be in the range of weak or very weak and not valid in this number of observations.

DISCUSSION

The considerable diversity of morphological, clinical manifestations and biological behavior of nosology, which became the subject of our study, underlies the difficulties of its differential diagnosis [10]. Analysis of publications, devoted TSGCT, showed that authors choose as the subject of study various aspects of etiology, pathogenesis, diagnostic algorithm for this tumor, approaches to surgical treatment and prospects for the use of targeted therapy. Thus, in a retrospective study of Korean traumatologists, the anatomical distribution of TSGCT was analyzed by magnetic resonance imaging (MRI) data and arthroscopy, since the anatomical scheme of the distribution of diffuse extracellular cells of TSGKP is known [15]. Research by the team of authors from the Department of Orthopedics, Central Southern University (China) aimed to determine the prognosis of patients with diffuse-type TSGCT with significant distribution within the joint, which was accidentally diagnosed during total knee arthroplasty [16].

Another work by Chinese researchers from the main laboratory of regenerative bone and cartilage medicine in Guangdong is devoted to a systematic multicenter retrospective analysis of the clinical characteristics of TSGCT. Their data included information about patients' gender, age, clinical presentation, localization, duration of symptoms, comorbidities, treatment strategy, recurrence, and routine laboratory data [6]. The authors analyzed the severity of the listed clinical and anamnestic data in groups of patients with TSGCT in the knee and the hip. A T-test was performed to evaluate differences in continuous variables. The chi-square test was used to evaluate differences between dichotomous variables.

In retrospective study by the team of authors from the Department of Pathology of the State Medical Research Institute (India), the determination of clinical and histopathological ratios in TSGCT taking into account the age of patients, sex, tumor localization, macroscopic features, size, clinical treatment [17]. However, a detailed study of the most characteristic histological features of TSGCT, the determination of the main reference points of morphological diagnostics, finding out with what frequency they occur and the dependencies of the severity of one feature in the presence or absence of another - were not conducted.

In our study, the focus was on determining the association between clinical symptom data, patient history, information on macroscopic cell structure, and individual morphological features that, in our opinion, most characterize the polymorphism of its histological structure. Analysis of the distribution of patients by age and gender showed that diffuse-type TSGCT is more common in women (60% of cases) and is characteristic of patients of young age (mean age – 35-37 years); the localization of the lesion is dominated by the knee – almost 2 \ 3 of all cases. In general, the results obtained do not contradict similar calculations presented in the recent work of researchers who studied this tumor [2, 3, 6, 9, 10, 17]. Symptomatic growth of TSGCT in the joint capsule characterized by pain, which is noted by the vast majority of patients (88%), pronounced limitation of movement in the joint (76%), which eventually leads to the development of contracture in the joint (63%). In every fourth patient there is a local increase of temperature near the affected joint, which is probably caused by concomitant synovitis. The diffuse type of TSGCT is characterized by the absence of a capsule in the cell, the expansion of nodular proliferates within the synovial membrane, which is accompanied in approximately 1 \ 5 cases by hypertrophy of synovial villi.

All cases of TSGCT were evaluated for signs of productive and exudative (mainly fibrinous) inflammation in

tumor tissue and density of macrophage-histiocytic infiltrates, the number of giant multinucleated cells, the severity of fibrillation growth of proliferate from synovium tumor cells in the form of nests, strands, chains, solid formations [18]. Morphological parameters, that we have identified, characterize pathological changes in the tissues of TSGCT; careful analysis of the frequency of their occurrence in the different comparison groups made it possible to establish intergroup differences and correlations between individual indicators, which were previously unknown or not obvious.

CONCLUSIONS

1. Pathomorphological features of the diffuse-type TSGCT indicates the predominance of diffuse proliferates of synovial cells in its structure on the background of thin fibrous immature fibrous stroma with signs of inflammation, high content of siderophages and insignificant number of multinucleated forms.
2. The closest correlation (positive dependence, in the range of average values of the association coefficient, reliable with the available number of observations) was found between the indicators «Cell size» and «Severity of hemosiderosis» and «The number of multinucleated giant cells»; «Presence of nodes» and «Kind of stroma»; «Presence of villous growths» and «severity of hemosiderosis».
3. Our study was determine to analyze of incidence rates and correlation relationships, revealed some previously unknown differences and dependencies that are important for understanding the pathogenesis, improvement of diagnosis and prognosis of diffuse-type TSGCT.

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Conflict of interest:
The Authors declare no conflict of interest

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FEATURES OF HEMODYNAMICS OF FETOPLACENTAL COMPLEX IN PREGNANT WITH PERINATAL INFECTIONS

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ABSTRACT

Introduction: Perinatal infections are an important issue in modern obstetrics, perinatal and pediatric care and one of the main causes of perinatal morbidity and mortality. The persistence of infection in the mother's body can lead to an adverse outcome of pregnancy and childbirth, but it does not always mean the infection of the fetus and the development of an infectious disease. The presence of foci of infection in the body of a pregnant woman is only one of the reasons for the development of intrauterine infection. Dopplerometric study in IUI promotes identification of patients at risk of developmental retardation and helps to determine the initial signs of fetal distress.

The aim: To study the features of hemodynamics of fetoplacental complex in pregnant with perinatal infections, depending on their implementation in newborns.

Materials and methods: The study involved examination of 230 couples of pregnant-newborns, who were divided into clinical groups: Group I - 60 couples with viral infection; Group II - 60 couples with bacterial infection; Group III - 60 couples with combined infection. Each clinical group was divided into 2 subgroups: with implementation of infection in newborns (1) and without it (0). Control group included 50 pregnant-newborns couples with physiological course of pregnancy and early neonatal period. Ultrasound (echographic and dopplerometric) study was performed according to the generally accepted technique on MINDRAY M7. The condition of the bloodstream was determined in the following vessels: umbilical artery, thoracic aorta, medial cerebral artery, uterine arteries. The resulting data was subject to statistical processing using the STATISTICA software.

Results: Pregnant of the control and main groups underwent ultrasound somatogenic study with a syndromological analysis. Assessment of indices of RI and PI in the I-III clinical groups showed a tendency to increase. These values in the main group were significantly higher than the normative ones. More severe violations of the blood flow were observed in Group I and III. More pronounced changes in utero-placental-fetal blood flow were recorded in pregnant women with the implementation of infection. Peak systolic velocity in the medial cerebral artery was 1.3 times higher in Group II, 1.8 times higher in Group I and 1.6 times higher in Group III than in women with physiological pregnancy.

Conclusions: Pregnant women of the main clinical group, in comparison with the normative indices of healthy pregnant, were found to have an increase in the indices of vascular resistance in the major vessels of the uterus-placental-fetal basin, which is likely due to the toxic effects of metabolic products of pathogens of infections that persist in the body on the endothelium of the blood vessels.

KEY WORDS: perinatal infections, hemodynamics, fetoplacental complex

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INTRODUCTION

Currently there is an increase in the incidence of perinatal infections (PIs) among obstetric and gynecological disorders. PI is an important problem in obstetrics, perinatology and pediatrics, and one of the main causes of perinatal morbidity and mortality [1.2.3].

The persistence of PI in the mother's body can lead to adverse outcomes in pregnancy and childbirth, but it does not always mean infection of fetus and the development of an infectious disease. The presence of foci of infection in the body of pregnant is only one of the reasons for the development of intrauterine infection (IUI) [4].

Despite extensive study of the problem of IUI, the reasons for the transition of infection to the infectious process are still not clarified. The latter is connected with the fact that the mechanism of development of the IUI is rather complex and many aspects of this problem remain controversial and require further study [5.6].

One of the leading factors in ensuring normal pregnancy, fetal growth and development are hemodynamic processes in a single system, «mother-placenta-fetus». Detection of changes in hemodynamic parameters reflects the degree of fetal distress.

To date, the nature of changes in vascular resistance in the «mother-placenta-fetus» system in pregnant, depending on their implementation and etiology is not fully determined.

Evaluation of the state of hemodynamics of the fetus in IUI is not a specific feature, but it is very important for determining the condition of the uterus that can be impaired, causing dysfunction of the fetoplacental complex (FPC) in pregnant with PIs. Therefore, dopplerometric study of FPC allows to select patients at risk of developing fetal growth retardation (FGR) and to determine the initial signs of fetal distress.

Uncomplicated course of pregnancy is characterized by an increase in endothelium-dependent vasodilation, which occurs under the action of such mediators as nitric oxide (NO), prostacyclin and hyperpolarizing factor of endothelial origin [7].

According to T.G. Sukhikh and co-authors, 2008, under the impact of infectious agents that can damage the vascular endothelium there is a significantly less release of relaxation factors, and the formation of vasoconstrictor factors remains or increases. There is also an imbalance between the mediators, which normally provide a normal relationship between the impact of all endothelial-dependent processes, first of all, between the discharge of vasodilating, on the one hand, and the content of vasoconstrictive prothrombotic factors, on the other hand [8]. This causes activation of inflammatory reactions, vasoconstriction, and changes in hemostasis parameters.

Endothelial dysfunction occupies a leading place in the development of hemodynamic disorders in the «mother-placenta-fetus» system. The role of endothelial dysfunction in the pathogenesis of development of gestosis, fetoplacental insufficiency, habitual miscarriage, intrauterine fetal infection has been proved [9].

Thus, the impact of infectious agents can be one of the manifestations of endothelium dysfunction and cause disturbances of its vasoregulative function: the disorder of the arteries' ability to expand and provide for normal flow of blood when necessary.

THE AIM

To study the features of hemodynamics of the fetoplacental complex in pregnant with perinatal infections, depending on their implementation in the newborn.

MATERIALS AND METHODS

The study involved 230 couples of pregnant-newborn. The subjects were divided into three clinical groups:
– Group I – 60 couples with viral infection;
– Group II – 60 couples with bacterial infection;
– Group III – 60 couples with combined infection.
Each clinical group was divided into 2 subgroups: with the implementation of infection in newborns (1) and without it (0). The control group included 50 couples of pregnant-newborns with a physiological course of pregnancy and an early neonatal period.

The PI was determined in the presence of high titres of anti-infective M antibodies and low-dose IgG in the test material (venous blood of pregnant women, umbilical cord blood obtained during labor, amniotic fluid, breast milk, maternal and fetal saliva, vaginal washings, vaginal secretion), presence of IUI signs in fetuses was determined according to the findings of ultrasound study of the FPC.

Ultrasonography (echographic and dopplerometric) was performed according to the generally accepted methodology on the MINDRAY M7 (China) device [10.11]. Dopplerometric study was performed using a sensor of 3-7 MHz, a frequency filter of 100 Hz and a test volume of 2 mm. The condition of the bloodstream was determined in the following vessels: umbilical artery (UmA), thoracic aorta (TA), medial cerebral artery (MCA), right and left uterine arteries (UA).

The study of the flow curves in the blood vessels of the arterial vessels implied the assessment of the peak systolic velocity (PSV), maximum systolic velocity (Vs), end diastolic velocity (Vd), and the time average velocity (Vav) with the subsequent calculation of the resistance index (RI) and pulsation index (PI). According to M.V. Medvedev, 2013, these indices are related to the angle-independent parameters and allow us to evaluate the size of the peripheral resistance [12].

The indices were calculated according to the formulas proposed by the authors [11]:
- PI = (Vs-Vd)/Vav,
- RI = (Vs-Vd)/Vs.
The comparative analysis of the flow curves in the right and left UA in the control group showed that vascular indices differed slightly to each other: the difference was 7.1 ± 0.2%. Since RI was lower than placental attachment, which, according to M.V. Medvedev, 2013, is associated with a higher level of vascularization, an assessment of the flow in the UA was carried out precisely on the side of the attachment of the placenta [12].

The resulting data was subject to statistical processing using the STATISTICA software. Quantitative indices were given as median (Me), interquartile range (LQ - lower quartile, UQ - upper quartile) and sample size (min - minimum value, max - maximal value) or in the form X ± m, where X is the mean value, and m is the standard error of the mean. The coincidence of the distribution of quantitative indices with normal in groups was evaluated by the Kolmogorov-Smirnov test. Since the law of the distribution of the numerical indices under study was different from the normal, the statistical significance was checked by non-parametric Mann-Whitney test (MWT) (in the case of paired independent populations) and the Kruskall-Wallis test (KWT) (in the case of multiple independent populations).

RESULTS AND DISCUSSION

The pregnant of the control and main groups underwent ultrasound somatogenic studies with syndromological analysis. There were no changes in the internal and provisory organs in the control group of pregnant women.

The echographic criteria for IUI according to ultrasound data were: ventriculo-, hepato- and gastromegaly, increased echogenicity of the endothelium of the internal and provisory organs, oligohydramnios, polyhydramnios, and the presence of hyperechogenic inclusions in amniotic fluid [13]. The presence of echographic markers of IUI showed evidence of a possible birth of a child with signs of intrauterine infection [14].

Pregnant women of the main group with the implementation of infection were at the same time found to have echographic changes in the internal organs, the amount of amniotic fluid and the state of the placenta [15].

During the study, features of utero-placental and feto-placental blood flow in pregnant with PIs were determined. Thus, the criteria for pathological flow were the

Table 1. Dopplerometric indices in the functional system «mother-placenta-fetus» in the control group

Dopplerometric index	Clinical group		
	Control group		
	Vessel under study		
	UmA	TA	UA
RI	0.66±0.05	0.76±0.08	0.48±0.15
PI	0.96±0.22	1.89±0.4	1.10±0.18

Table 2. Dopplerometric indices in the functional system «mother-placenta-fetus» in pregnant of Group I and II

Dopplerometric index	Clinical group					
	I			II		
	Vessel under study			Vessel under study		
	UmA	TA	UA	UmA	TA	UA
Implementation of infection						
RI	0.80± 0.03*	0.91± 0.02*	0.75± 0.04*	0.74± 0.03**	0.87± 0.02**	0.67± 0.04**
PI	1.44± 0.085*	2.65± 0.12*	1.64± 0.12*	1.27± 0.085**	2.41± 0.12**	1.40± 0.12**
Without implementation of infection						
RI	0.76± 0.03*	0.86± 0.02*	0.69± 0.04*	0.70± 0.03**	0.82± 0.02**	0.61± 0.04**
PI	1.43± 0.085*	2.54± 0.12*	1.61± 0.12*	1.25± 0.085**	2.39± 0.12**	1.37± 0.12**

*,** – Differences between Group I and II at statistically significant level p <0.01 (MWT).

Table 3. Dopplerometric indices in the functional system «mother-placenta-fetus» in the pregnant of Group III

Dopplerometric index	Clinical group		
	III		
	Vessel under study		
	UmA	TA	UA
Implementation of infection			
RI	0.86±0.03***	0.95±0.02***	0.83±0.04***
PI	1.61±0.085***	2.89±0.04***	1.88±0.12***
Without implementation of infection			
RI	0.82±0.03***	0.90±0.02***	0.77±0.04***
PI	1.59±0.085***	2.78±0.04***	1.85±0.12***

*** – Differences between Group II and III at statistically significant level p <0.01 (MWT).

discrepancies between the RI, PI with similar indices of the control group (Table 1 - 3).

Assessment of indices of RI and PI in the main clinical group showed a tendency to increase. These values in the main group were significantly higher than the normative ones. More severe violations of the blood flow were observed in Groups I and III, which can be explained by the tropism of the circulating viral infection to the endothelial cells. Moreover, more pronounced changes in the utero-placental-fetal blood flow were observed in pregnant with the implementation of infection.

The study showed a significant increase in the PSV in MCA in all studied groups with PIs as compared to the corresponding parameters of the control group (KWT, MWT, p <0.001) (Fig. 1).

Thus, PSV in the MCA in the control group was as follows: the median value of this index was 81.15 cm / s, the interquartile range was 65.80 ÷ 123.50 cm/s. In Group I the median value of PSV in the MCA was 148.57 cm/s, the interquartile range was 139.06 ÷ 158.04 cm/s, in Group II the median value was 106.55 cm/s, the interquartile range was 94.70 ÷ 117.05 cm/s, in Group III the median value was 127.56 cm/s, the interquartile velocity was 58.70 ÷ 147.08 cm/s. Thus, the findings suggest that the PSV in the MCA is 1.3 times higher in Group II than in

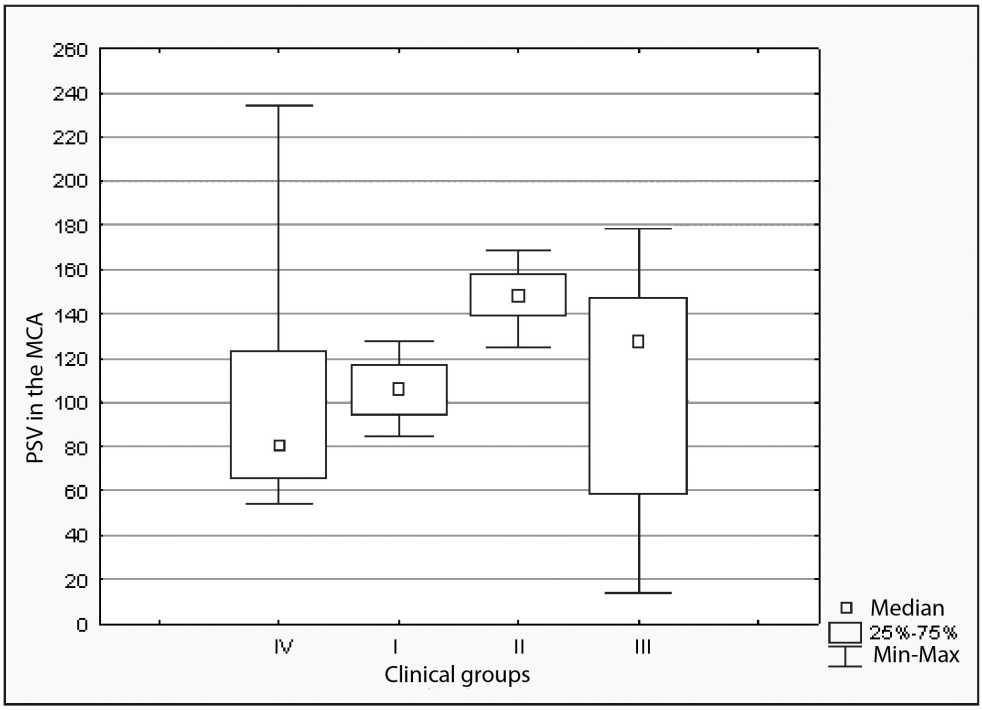

Fig. 1. Boxplots of PSV dependence in the MCA in the groups under study

women with physiological pregnancy, 1.8 times higher in Group I and 1.6 times higher in Group III. There were no statistically significant differences between groups with and without infection.

Consequently, pregnant women with PIs were found to have an increase in the level of vascular resistance indices in UmA, CA and UA secondary to an increase in PSV in the MCA. It is known that the increase in the indices of vascular resistance in the UmA may be associated with a decrease in the vascularization of terminal chorionic villi [16]. The change in velocity in the MCA may induce hypoxic-ischemic lesions of the central nervous system [17], and, according to authors [18], lead to deviations in the psychomotor development of newborns.

Since blood flow in the FPC was not registered in any of the pregnant women and there was no critical blood circulation (zero or reversible), it can be assumed that their fetuses were in a state of chronic hypoxia.

Impairments in the feto-placental and utero-placental blood flow indicate that PIs cause the development of fetal intrauterine hypoxia. The most pronounced signs of fetal distress were manifested in Groups I and III, especially in subgroups with implementation of infection.

CONCLUSIONS

Pregnant of the main clinical group, in comparison with the normative indices of healthy pregnant women, were shown to have an increase in the indices of vascular resistance in the major vessels of the uterus-placental-fetal basin, which is likely due to the toxic effects of metabolic products of pathogens of infections that persist in the body on the endothelium of the blood vessels.

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NEUROPHYSIOLOGICAL CHARACTERISTICS OF PSYCHOSOMATIC DISORDERS AND PSYCHOSOMATIC PATHOLOGY IN CHILDREN AND ADOLESCENTS

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ABSTRACT

Introduction: In this article neurophysiological aspects of the formation of psychosomatic disorders (PSD) and psychosomatic pathology (PSP) in children and adolescents are presented.

The aim of the study was to determine neurophysiological characteristics in healthy children and adolescents and patients with PSD and PSP based on the analysis of their electroencephalogram (EEG).

Materials and methods: In total 59 children aged between 11 and 18 years old were examined, among them 24 with PSD (duodenal ulcer and bronchial asthma) (Group I), 15 patients with PSP (irritable bowel syndrome) (Group II), and 20 healthy children of the corresponding age (III Control group). A complex neurophysiological diagnosis with topographic mapping of the spectral power of the main EEG rhythms and its spectral analysis was carried out.

Results: In patients with PSD, a dominant bimodal spectrum of the alpha rhythm of EEG with a normal or partially lost topical distribution was observed. While in patients with PSP, a disorganized spectrum of the alpha rhythm power at the EEG with distorted zonal distribution was detected. These findings allow determining characteristic EEG signs of risk for the PSD and PSP formation in children.

Conclusions: Spectral-topographic analysis of EEG could be used for neurophysiological rapid diagnostics of the functional state of the brain, objective control of treatment and rehabilitation measures, and prediction of PSD to PSP transformation in children.

KEY WORDS: psychosomatic disorders, psychosomatic pathology, children, electroencephalography

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INTRODUCTION

According to the theory of functional systems (FS) of the academician P.K.Anokhin, the sanogenetic and protective reactions of an organism are always excessive in the relation to the induced reactions that they cause, and therefore, they are potentially pathogenic. Thus, the protective (sanogenetically–compensatory) reaction, under appropriate conditions, could be transformed into a pathogenic link of a disease [1, 2, 3, 4, 5].

It is known that the basis of every FS is to remain within certain limits, or to change the indicators of body functions in order to optimally support their adaptive and sanogenetic responses. In order to achieve this result, a selective mobilization of regulatory mechanisms at all levels of structurally-functional organization takes place and the achieved result becomes a system-forming factor [1, 2, 3, 4, 5].

To date, the concept of emergency compensation has been established, as a genetically determined response of regulatory systems, which aimed to restore optimal adaptive parameters in conditions of interaction between the organism and the etiological factor. At the same time, the cause of the disease contributes to dysregulation of a FS with a lack of energy in the executive organs, which results in the violation of homeostasis and directly implements the pathogenicity of the etiological factor [4, 6, 7].

As a result of the formation of pathological neural integrations, which are absent in physiological conditions, the plasticity of the nervous regulatory apparatus of a FS decreases. Such integrations include: a generator of excessively intensified excitation, as the basis of the pathological determinants of the abnormal system of nervous regulation, pathological dominant, and the pathological system of regulation of the central nervous system (CNS) itself.

Principal provision of the P.K. Anokhin's theory is the recognition of the two-way communication of FS with the environment, which is determined by specific system processes [1, 2, 5, 8, 9]. In addition, the concept of "neurofunctional system" is distinguished as a stable (in a certain period of time) integral structure of neurophysiological processes, which corresponds to the concept of syndrome in medicine [10].

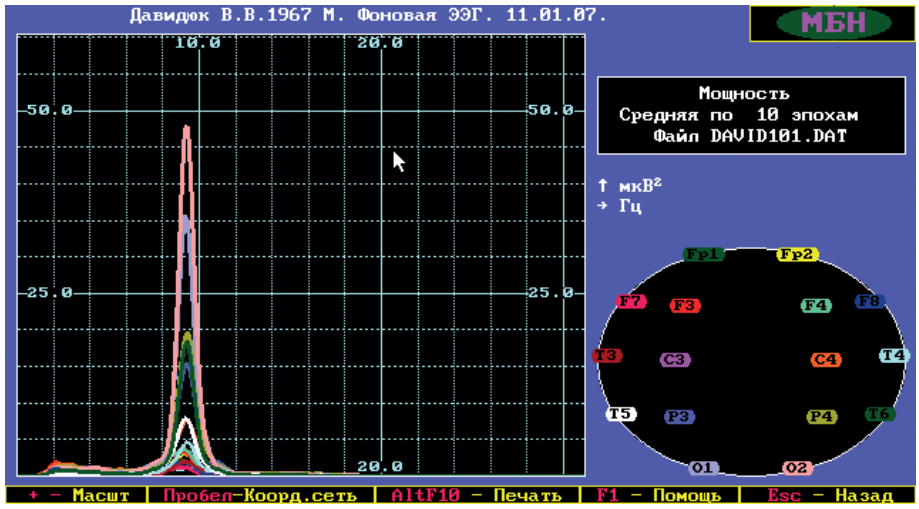

Figure 1. Spectogram of the main EEG rhythms. Organized type of EEG (1 group) was detected. A dominant monomodal spectrum of the alpha rhythm power was observed.

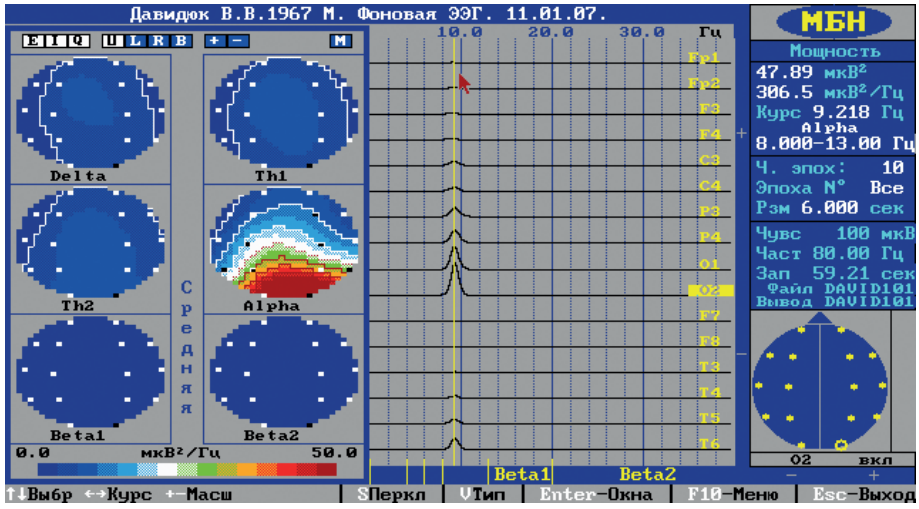

Figure 2. Maps of the spectral power of the main EEG rhythms. Organized type of EEG (I group)- a dominant monomodal spectrum of alpha rhythm power (maximum spectral density of alpha-rhythm in the occipital regions of the cerebral cortex)

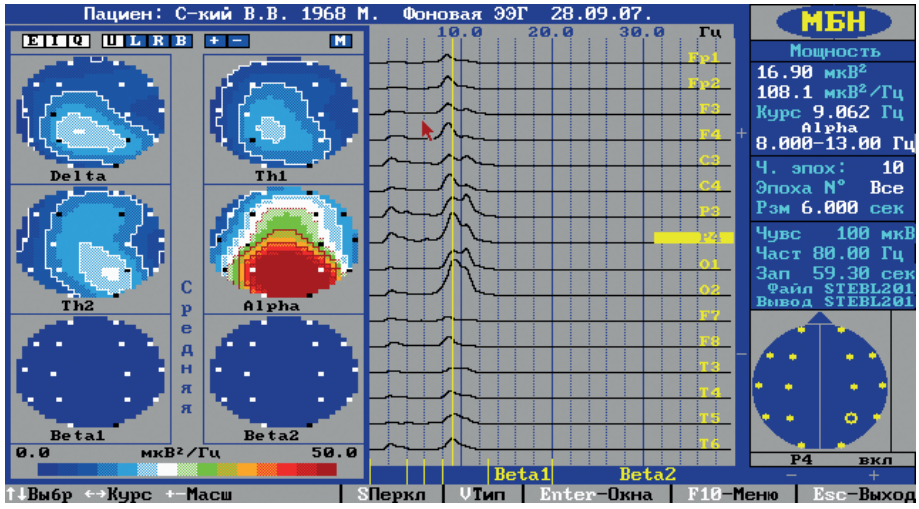

Figure 3. Spectogram of the main EEG rhythms. Moderately disorganized type of EEG (II group). A dominant bimodal spectrum of alpha rhythm power was observed.

Thus, there is a system of mental and neurophysiological processes that cause work of the brain in the form of electrical impulses, which are registered by the method of electroencephalography (EEG) with graphical display in a real time [11, 12, 13].

The key parameters in assessing results of EEG are rhythms of the brain, which differ in form, permanence, periods of oscillation and amplitude [12]. Their regularity reflects normal coordinated activity of various structures of the central nervous system. In a healthy individual, each type of (alpha, beta, delta and theta) rhythms has its own set of characteristics and captures the specific activities of the brain. Thus, the alpha rhythm is most intense in a state of rest in the areas of the nape and vertex

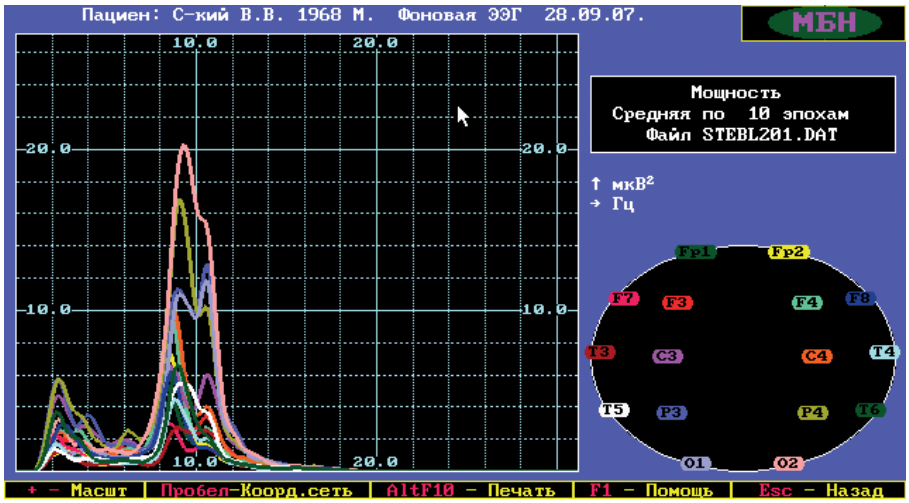

Figure 4. Maps of the spectral power of the main EEG rhythms. Moderately disorganized type of EEG (II group) - a dominant bimodal spectrum of alpha rhythm power, with normal or partially lost topical distribution (maximum spectral density of the alpha-rhythm in the occipital- parietal regions of the brain cortex).

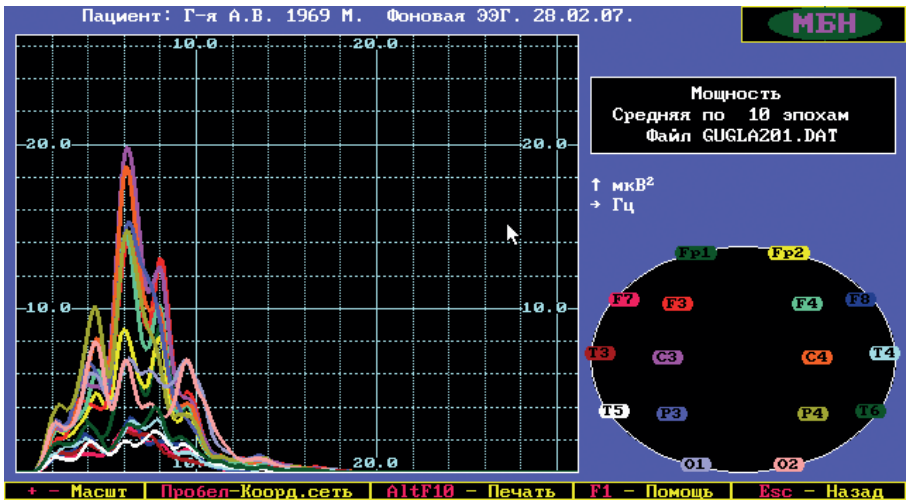

Figure 5. Spectogram of the main EEG rhythms. Disorganized type of EEG (III group) was detected. A visible (not dominant), disorganized, polymorphic spectrum of alpha rhythm power with low spectral density was observed. The amplitude of the spectral power of the delta and theta-constituents of EEG were 2.3 ± 0.2 (in case of hyperventilation 4.2± 0.4) times higher than the amplitude of the spectral power of the alpha rhythm.

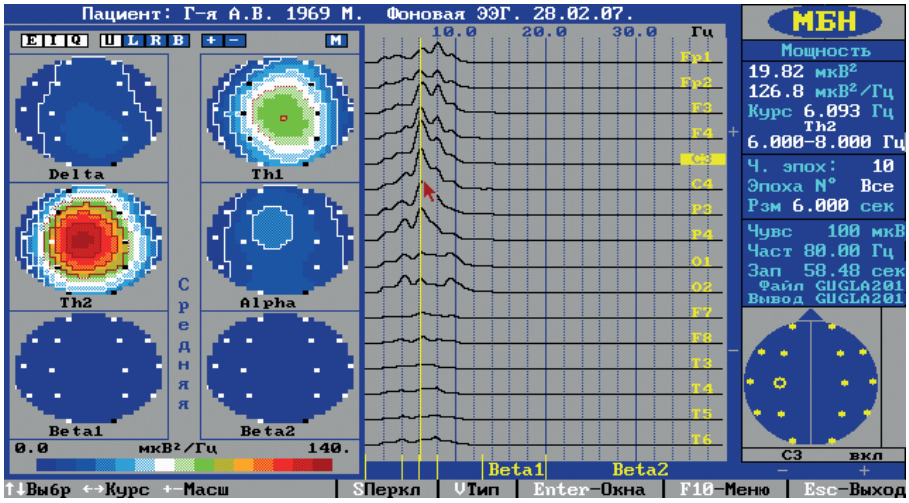

Figure 6. Maps of the spectral power of the main EEG rhythms. Disorganized type of EEG (III group) was detected. A visible (not dominant), disorganized, polymorphic spectrum of alpha rhythm power with distorted zonal distribution (maximum spectral density of alpha-rhythm in the central lobes of the brain cortex) was observed.

with frequency of 8-14 Hz and amplitude up to 100 μV. The beta rhythm is an indicator of the active work of the brain and its normal frequency in both hemispheres is 14-30 Hz, and the amplitude is 3-5 μV with the highest intensity in the frontal lobes. The delta and theta rhythms have frequency of 1-4 Hz and 4-8 Hz at amplitude of 40 μV and up to 30 μV, respectively, and characterize sleep of a healthy person.

The interpretation of the EEG includes the assessment of the sustainability of brain rhythms, simultaneous activity of

the neurons of both hemispheres and the response to routine functional tests ("opening-closing of eyes ", "photostimulation," "hyperventilation").

In various pathological conditions, nerve cells pass to another level of functioning, which is reflected in their electrical activity, and transformation in the system of connections and manifestations on EEG [13].

The electrical activity of the brain is formed under the influence of two main factors: local and remote. Local factors include blood circulation, gas composition of blood, liquor dynamics, and composition of liquor, which determine the metabolism of neurons. While remote factors are: flow of the nerve impulses that bind the cortex and subcortex, cortical divisions between themselves, specific and non-specific effects on the brain cortex with formation of changes in EEG parameters [11]. Nosologically, they are not specific and indicate only change in the functional state of cell populations and synaptic formations, which can be analyzed in healthy children, as well as in children with psychosomatic disorders (PSD) and psychosomatic pathology (PSP). The response of FS can be determined by its ability to compensate for the specified lesions [12].

THE AIM

The aim of the study is to determine the neurophysiological characteristics of healthy children and adolescents and patients with PSD and PSP based on the analysis of their EEG parameters.

The study was carried out within the framework of the project «Conducting an expert assessment of the needs of children, as well as the development of individual child care plans» with the support of UNICEF.

MATERIALS AND METHODS

From December 2014 to March 2017, we conducted a clinical and neurophysiological study at the Children's Clinical Hospital No. 9 in Kyiv, which did not contradict the Declaration of Helsinki and received positive feedback from the Ethics Committee of Schupyk National Medical Academy of Postgraduate Education.

In order to study of clinical-neurophysiological associations, 59 children aged 11 to 18 years old (mean age 15.6 ± 0.5 years) were examined. Particularly, 24 patients with PSP (duodenal ulcer (DU) and bronchial asthma (BA) (Group I), 15 patients with PSD (irritable bowel syndrome) (Group II) and 20 healthy children of the corresponding age (III control group) were examined.

The main diagnoses in patients were verified in accordance with the ICD-10 and in accordance with the Unified Protocols of the Ministry of Health of Ukraine No. 53 of January 31, 2013 and No.868 dated 8.10.2013 [14, 15]. All the subjects underwent complex neurophysiological diagnostics using topographic mapping of the spectral power of the main EEG rhythms and its spectral analysis. The background EEGs were recorded from the anterior and posterior, frontal, central, parietal, occipital and temporal regions of the brain according to the generally accepted international system "10-20" (H.Jasper, 1958).

Registration of the brain biopotentials was carried out using a 16-channel EEG-16 S "MEDICOR" (Hungary) electroencephalographer in a darkened, shielded, and sound-proofed chamber. Reactions of brain biopotentials during functional tests: "opening-closing of eyes" and hyperventilation (3 minutes) were investigated. Simultaneously with the EEG record on paper, it was registered and processed on the computer complex "Нейрокартограф 3.7" (МБН company, Russia). The automated analysis of the EEG was carried out in a monopolar system of leads and included a fast Fourier transform with subsequent calculation and processing of the power spectra of its basic rhythms for each of 16 leads (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6) and the construction of a brain map.

As an indifferent electrode, 2 ear electrodes (A1 and A2) were used. Power spectra were analyzed in the frequency band from 1 to 30 Hz, with a frequency of poll of 80 Hz for 60-second segments of unreflective EEG (10 episodes of analysis for 6 sec. each). The whole hardware and software complex underwent a metrological check and had a corresponding certificate.

In the study of the functional state of the brain the indicators of its bioelectric activity (BEA) were considered as informative and objective parameters.

The spectral characteristics of the main EEG rhythms and their topographic mapping were studied as the most adequate and most effective parameters in the screening and control of bioelectric activity of the brain in patients [11, 12].

Statistical analysis of the obtained results is carried out by generally used statistical methods (Bonferroni, T-test, IBM SPSS Statistics 22).

RESULTS AND DISCUSSION

The spectral analysis of EEG records of healthy children showed its organized type (Fig. 1 and Fig. 2) with domination of a regular alpha rhythm with stable frequency (10 vibrations / sec.), medium and high amplitude (60 to 100 μV), high power (up to 50 μV2) and its mono-modulation, with distinct zonal differences and insignificant (<20%) interhemispheric asymmetry in amplitude of the spectral power, usually on the right. The shape of α-waves was normal, b-activity was of low frequency (within 13-20 Hz) and of low amplitude (up to 15 μV) in small quantities with maximum spectral density of brain maps in the frontal lobes of the brain cortex. D-activity with frequency of 2-4 oscillations / sec. was of an average amplitude (up to 40 μV) in moderate quantities, with maximum spectral density in the posterior-frontal and occipital regions of the cerebral cortex. q-activity with frequency of 5-7 oscillations / sec. was of an average amplitude (up to 40 μV) in moderate quantities, with a maximum spectral density in the posterior-frontal areas of the brain cortex.

The response for "opening-closing eyes" test was adequate (there was a distinct depression of alpha rhythm). The reaction of rhythm assimilation during discrete light stimulation was expressed in the frequency range of 9-15 Hz. Hyperventilation did not provoke an increase of a spectral power.

Patients with PSD (with irritable bowel syndrome) had a moderately disorganized type of EEG (Fig. 3 and Fig. 4) with domination of irregular alpha rhythm with unstable frequency (9-11 oscillations / sec.) and bimodal spectrum of its power, low and medium amplitude (40 to 60 μV), average energy power (up to 20 μV2), weakened alpha rhythm modulation, in some cases with ill-defined zonal discrepancies, with significant (> 20%) interhemispheric asymmetry of the amplitude of spectral power. The shape of the α-waves was acute, b- activity was of low frequency (within 13-20 Hz) and with low and medium amplitude (up to 25 μV) in a significant quantities, with a maximum spectral density in the frontal and occipital regions of the cerebral cortex. D- activity with frequency 2-4 oscillations / sec. was of a medium and high amplitude (up to 60 μV) in great quantities, with a maximum spectral density in the posterior-lobe-central and the occipital lobes of the cerebral cortex. q-activity with frequency 5-7 oscillations / sec. was of a medium and high amplitude (up to 70μV) in great quantities, with a maximum spectral density in the posterior-frontal-central regions of the brain.

The response for "opening-closing eyes" test was adequate (low alpha-rhythm depression). RPD during discrete light stimulation was expressive in the frequency range of 8-10 Hz.

Hyperventilation provoked a slight increase in the spectral power of the slow (delta and theta) components of the EEG.

In patients with bronchial asthma-BA and duodenal ulcer-DU, a disorganized type of EEG was found (Fig. 5 and Fig. 6) which was characterized by irregular disorganized alpha rhythm with unstable frequency (8-10 oscillations / sec.), polymorphic spectrum of the alpha rhythm power, of a low amplitude (up to 35 μV), and low and average energy power (up to 10 μV2), without modulation of the alpha rhythm, in some cases with distorted zonal differences and significant (> 20%) interhemispheric asymmetry of the amplitude of spectral power. The shape of the a -waves was acute, b- -activity of a low and high frequency (within 13-30 Hz) and medium and high amplitude (up to 30 μV) in significant quantities, with a maximum spectral density in the frontal-central and the occipital lobes of the cerebral cortex.

D-activity with frequency of 2-4 oscillations/ sec. with medium and high amplitude (50-80 μV) in great quantities, with a maximum spectral density in the posterior-lobe-central and occipital lobes of the brain cortex.

q-activity with frequency 5-7 oscillations / sec. of α medium and high amplitude (up to 100 μV) in a large number, with a maximum spectral density in the posterior-frontal-central lobes of the cerebral cortex.

At the same time, the amplitudes of the spectral power of the slow constituents of the delta and theta-ranges were 2.3 ± 0.2 times higher than the amplitude of the spectral power of the alpha rhythm.

The response of "opening-closing eyes" was weakened (small unexpressed alpha-rhythm depression).

RPD during discrete stimulation was expressive in the frequency range of 7-9 Hz.

Hyperventilation provoked a significant increase (in 4,2 ± 0,4 times) of the spectral power of the slow (delta and theta) components of the EEG, in the form of bialaterally synchronous, paroxysmal waves of frequency 4-7 oscillations/ sec, with a maximum spectral density in back-frontal-central lobes of the cerebral cortex. In some cases, with signs of generalization and the phenomena of the involvement of the diencephalon and brain stem structures.

Consequently, the analysis of neurophysiological characteristics of the brain showed that the most optimal for screening-control of its functional state in patients with PSP was the study of its bioelectric activity using the spectral-topographic analysis of the basic EEG rhythms, and the construction of spectral power map.

After examining the features of the functional state of healthy children with an organized type of EEG, we concluded that in this group, there were individuals with normal spectral and topographic parameters of EEG, in accordance with the age norm, with physiological indicators of the functional state of the brain that provided psychological and physical health.

Neurofunctional state of children with PSD differs by moderately-disorganized type of EEG. In this group, patients with partially abnormal spectral-topographic EEG parameters predominate, with moderately altered parameters of the functional state of the brain, which can be considered as one of the risk factors for the formation of PSP.

Features of the neurofunctional state of the brain of children with BA and DU were the following: a disorganized type of EEG with pathological, distorted spectral and topographic characteristics, significantly changed characteristics of the functional state of the brain, which might be the reason for the formation of PSP.

CONCLUSIONS

1. In healthy children and adolescents, the dominant monomodal spectrum of the alpha rhythm of EEG, with normal topical distribution (maximal spectral density of the alpha rhythm in the occipital lobes of the cerebral cortex) was observed.
2. In patients with PSD, the dominant bimodal spectrum of the alpha rhythm at EEG was determined, with normal or partially lost topical distribution (maximal spectral density of the alpha rhythm in the occipital-parietal and central lobes of the brain cortex).
3. In patients with PSP a disorganized spectrum (non-dominant) of alpha rhythm power of EEG was observed, with distorted zonal distribution (maximum spectral density of the alpha rhythm in the central regions of the cerebral cortex).

4. The aforementioned spectral-topographic parameters of the EEG analysis allowed the detection the characteristic EEG signs of risk for the PSD and PSP formation in children with high probability and stable reproducibility.
5. Spectral-topographic analysis of EEG could be used for rapid neurophysiological diagnostics of the functional state of the brain, objective control of treatment and rehabilitation measures, and determination of the prediction of the transformation of the PSD in the PSP in children.

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EVALUATION OF INDICATORS OF ENDOTHELIAL DYSFUNCTION AND INTRACARDIAC HEMODYNAMICS OF THE LEFT VENTRICLE IN PATIENTS WITH CHRONIC PULMONARY HEART BRONCHOPULMONARY GENESIS OF COMORBIDITY WITH ESSENTIAL ARTERIAL HYPERTENSION

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is the main cause of progression chronic pulmonary heart (CPH), it is a serious worldwide problem. The combination of COPD with essential arterial hypertension (EAH) ranges from 4 to 27.7% with increasing age.

The aim: To evaluate endothelium function changes by the level of metabolites of nitric oxide, endothelin-1(ET-1), values of ultrasonic diagnosis of the humeral artery (HA), intracardial hemodynamics of the left ventricle in patients with CPH in combination with EAH.

Materials and methods: The research is involved 175 patients. Indicators of endothelial function by the level of nitric oxide metabolites, ET - 1, ultrasound intracardiac hemodynamics of the left ventricle of the heart were studied.

Results: The patients with CPH in combination with EAH in compensation stage have reduced level of nitric oxide in comparison with patients with CPH without EAH and healthy. To a large extent, reducing of nitric oxide level in decompensation stage indicates about contribution of combined pathology and requires ED correction. On the contrary increased concentration of ET-1 in decompensation stage indicate about combined pathology and demands correction of endothelial cell function.

Conclusions: Thus, patients with CPH in combination with EAH are characterized by more pronounced changes in endothelial dysfunction toward an increase in the level of vasoconstrictor factors, a decreasing of vasodilators, which is confirmed by ultrasound diagnosis of HA and reflected in the peculiarities of the intracardiac hemodynamic state.

KEY WORDS: chronic pulmonary heart, comorbidity, endothelial dysfunction, internal cardiac hemodynamics

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INTRODUCTION

For the global community of respiratory disease is a global health problem, primarily because of their widespread prevalence among the able-bodied population, the constant progression, the development of frequent various of extra-pulmonary pathologies and effects. Nowadays known probably 80 diseases are cause of CPH. But the main cause of progression CPH is COPD that represents a major global challenge. Also it is devastating pathology that reduce patients' quality of life and is a huge socio-economic burden for morbidity and mortality worldwide [1,2]. As reported by definition of Havrysyuka V.K. [3], CPH is circulatory failure syndrome with the progressing of peripheral edema, which complicates the course of many diseases with damage to the structure or only lung function. There are two types of CPH: compensated as a sign of the basic disease and decompensated is a sign of peripheral edema. According to modern data in the world about 600 millions of patients with COPD that increasing with age. Before forecasts of experts, COPD will take on the third place among of structure cause of mortality by 2020 year [4,5,6,7,8].

According to the results of large screening studies, the prevalence of COPD is greater in smokers than in non-smokers, in people over 40 years of age more than in young people, in men more than in women. At the same time, society has little knowledge of this problem and the cost of scientific research COPD is in 13th place.

Published articles in European White Book of Lungs (2013 year) are once confirms this pattern. Considering the high prevalence of COPD, the number of patients with CPH as its complication increased. As a result of this complication, the mortality rate is 67% and ranks third after arterial hypertension (AH), coronary heart disease (CHD), particularly among the causes of death of persons over 50 years of age. According to the concepts of the global strategy of diagnostic, treatment and prevention of COPD (Global Initiative for chronic obstructive pulmonary disease, GOLD (2017) [9], COPD is a disease with significant extrapulmonary manifestation such as arterial hypertension (AH), CHD , metabolic syndrome (MS), obesity, etc. They significantly complicate not only the course of the disease, but also lead to a deterioration in the quality of patient's life. COPD becomes not only a

pulmonary problem, but also a cardiac due to the frequent progressing of cardiovascular comorbid pathology in this category of patients [10,11].

The comorbidity of COPD and EAH remains the most important, their combination ranges from 4 to 27.7%, in the older age groups up to 62%, it increasing with age [12]. This has a significant impact on health, quality and life expectancy. Recently, in the pathogenesis of CPH of bronchial pulmonary genesis, AH, CHD pay much attention for studying endothelial dysfunction as a pathogenetic link of these diseases [13,14,15,16]. Activation or damage of the endothelium is fundamental in the development of a wide range of pathological processes.

THE AIM

To evaluate changes in endothelial function by the level of metabolites of nitric oxide, endothelin -1 (ET-1), indicators of ultrasound of the humeral artery (HA), intracardiac hemodynamics of the left ventricle (LV) in patients with CPH of bronchopulmonary genesis in combination with essential arterial hypertension (EAH).

MATERIALS AND METHODS

The study involved 96 persons with CPH in combination with EAH, II stage (the main group), from their the stage of compensation was detected in 32 (33.3%) patients is group 3 without heart failure (HF), stage of decompensation have 64 (66.7%) patients is group 4 with signs of HF. The comparative group consisted of 64 patients with CPH have identical gender, age, severity of illness of their 32 (50.0%) patients have the stage of compensation 0 without signs of HF is group 1 and 32 (50.0%) in the stage of decompensation with signs of HF is group 2. Thus, were 34 females and 62 males with an average age of 57.5 ± 1.2 years. The control group for patients with CPH with EAH were 15 healthy identical in gender and age. The basis for the causing of CPH was COPD.

The day before, all patients has signed an informed consent to be participation in the research in accordance with the requirements of the 1975 Declaration of Helsinki, its revision in 1983 and Order of the Ministry of Health of Ukraine № 690 of September 23, 2009 «About approval of the procedure for conducting clinical trials of medicinal products and examination of materials of clinical trials» and « The typical provision for ethics committees». Ethical and the moral and legal aspects of the research were agreed by the commission of bioethics in Ukrainian medical stomatological academy.

The total content of the stable metabolites of nitrogen oxide was determined in blood serum by the spectrophotometric method by the set of reactants (Total NO) made by "RL-system", USA in accordance with the kit instructions. Determination of ET-1 level was carried out by the enzyme immunoassay by the set of reactants BIG Endothelin-1 (HUMAN), Peninsula Laboratories inc., Division of Bachem.

An Aloca 5000 Pro Sound (Japan) ultrasonic scanner with a 13 MHz line sensor according to the D.S. Celermayer method was used to measure the diameter of the vessel. The research was carried out in the morning fasting before taking medicines in a special room. The study of the right HA was carried out 2-5 cm above the elbow joint, the cuff of the tonometer was applied on the forearm. The diameter of HA (mm) was measured in the transverse and longitudinal planes in order to obtain the same values to improve measurement accuracy, the location of the sensor was noted. The diameter of the HA was defined as the distance between the anterior and posterior walls of the artery on the face of the vessel intima/flow. The diameter measurement was carried out at the finite-diastolic phase of the blood flow, which was determined at the moment of appearance of the tooth R on the ECG synchronized with the ultrasonic image. Endothelium-dependent vasodilation (EDVD) was determined for 90 seconds after 5 minutes of shoulder compression with 300 mm Hg pressure by calculating the percent change in artery diameter with initial. Endothelium independent vasodilation (EIVD) was determined as the maximum percent artery expansion within 5 minutes after sublingual administration of 0.5 mg of nitroglycerine at minute-by-minute registration. The norm considered increasing the diameter of vessels more than 10% of the initial and 20% against the background of nitroglycerine action.

The assessment of the state of intradermal hemodynamics of LV was carried out using two-dimensional echocardiography on Toshiba SSA, 380 A Powervision (Japan) according to a conventional technique.

The following parameters were determined: left atrial diameter (LA, mm), cardiac (l/min (m^2) and percussion (ml/m^2) indices (CI and PI, respectively), thickness of the posterior septum of LV (TPWLV, mm), emission fraction (EF,%), maximal rate of transaortal blood flow(Vmax, m / s). The diastolic function of LV was evaluated by Doppler investigation of the transmitral blood flow of early E (m/s) and late A (m/s), their E/A ratio (conventional units), isovolumic relaxation time (IVRT) and the size of the interventricular septum (IVS, mm).

The criteria for diagnostics COPD were approved by the order of the Ministry of Health of Ukraine of № 555 from 27.06.2013 "About approval and introduction of medical and technical documents on standardization of medical care in case of chronic obstructive pulmonary disease" (order with change №270 from 16.04.14 "About amendments to the orders of the Ministry of Health of Ukraine "[17]. The severity of COPD was consistent with stage II and stage III and stage II pulmonary insufficiency (LF). The severity of COPD was in stage II-III pulmonary failure (PF).

The examination of EAH patients was carried out in accordance with order №384 from 24.05.2012 by Ministry of Health of Ukraine "About approval and introduction of medical and technological documents and standardization of medical care for arterial hypertension" [18]. The classification of the Association of pulmonologists and cardiologists of Ukraine was used to assess heart failure (HF) in patients with CPH. According to which CI of 1 stage is found in 6 (6.3%) patients, HF of II stage in 84 (87.4%) and HF of III stage in 6 (6.3%) patients.

The criteria for exclusion from the study were the presence of symptom hypertension, complications of EAH, endocrine diseases requiring correction, kidney pathology, systemic diseases of connective tissue, oncological diseases and other conditions. Statistical processing of the results was carried out by the method of parametric statistics.

The Student test was used to assess the significance of the differences. The difference of the indicators was accepted reliably at (P<0,05), as well as with the nonparametric Kolmogorov - Smirnov criterion. Correlation analysis was performed by a linear Pearson correlation coefficient method on a Celeron 650 computer with software SPSS11,0.

RESULTS AND DISCUSSION

Should note that the study of nitric oxide in the pathogenesis of EAH revealed a decrease in basal and stimulated production of NO [19]. Nitric oxide has proved ineffective in relaxing smooth muscles or reduced endothelium ability at all by its production. The patients with CPH with combined pathology (third, fourth groups) have the nitric oxide content metabolites was significantly reduced compared to patients with CPH without EAH. Thus, the 3rd group it has 16.2 ± 1.3 mmol / l (P_1<0.05), in the 4th group - 13.1 ± 1.2 mmol / l (P_2<0.05), whereas the patients with isolated CPH have in the 1st group - 26.5 ± 1.2 mmol / l (P_1 <0.05), in the 2nd group - 20.2 ± 1.1 mmol / l(P_2<0,05), the healthy persons have 36,3±0,8 mmol / l. So, the rate decreased by 10.3 and 7.1 mmol/L compared to the group of CPH patients without EAH and healthy individuals. The comparison of indicators of the 3rd and 4th group (CPH with EAH) reliable a difference between them - 3.1 mmol/l (P_3*/ ≠) that demonstrates that progressing of HF considerably influences damage of function of endotheliocyte, reducing synthesis of a vasodilator of nitrogen oxide. Its effect should be considered alongside ET-1 in these patients. According to the data obtained, in patients with CPH in combination with EAH in the stage of compensation (3rd group) the level of ET-1 was 5.2 ± 0.1 mmol / l, in decompensation (4th group) - 7.8 mmol/l. Whereas in patients with CPH without EAH, respectively, 4,0 ± 0,4; 6.2 ± 0.6 mmol/l. It increased significantly by 1.2 ± 0.09 mmol/l (P_1<0.05) in 3rd group and by 1.6 ± 0.06 mmol/l in 4th group. According to the obtained data, even in patients with CPH without signs of EAH in the stage of decompensation, along with the decrease of NO metabolites, an increase of ET-1 is observed, and especially in the combination of pathology in the stage of decompensation (7.8 mmol / l), i.e. 1.9 times more than for CPH in the non-EAH compensation phase.

This may indicate that several factors, such as arterial hypoxemia, increased intra-thoracic pressure (all patients had emphysema), and abnormal hemodynamics in the small circulatory tract, which are already characteristic for patients with COPD without CPH are important in the pathogenesis of these shifts. This is confirmed by the high degree of correlation in these patients between SaO2 and the level of metabolites of nitric oxide, ET-1. Studying the parameters of the morphometry of HA, we again indirectly evaluate the indices of nitric oxide. Therefore, to further study the state of endothelial dysfunction (ED), we conducted a non-invasive morphometric research of HA. patients with CPH without EAH in comparison with the group of healthy individuals already notice changes in the parameters of morphometry of HA. Thus, the initial diameter of HA in these patients in the stage of compensation increased by 1.3 ± 0.002 mm (P<0.05) in the stage of decompensation - by 1.6 ± 0.01 mm (P<0.05).

Significantly decreased in patients of the 2nd group of EDVD (by 5,0%, P<0,05), the initial rate of blood flow and increased the rate at hyperemia (P<0,05).

The significantly wider initial diameter of HA was determined in patients with CPH and EAH, such as, the 3rd group by 0.5 mm (P_1< 0.05); the 4th group by 0.8 mm (P_2<0.05) in comparison with patients with isolated CPH (1st and 2nd group). There were lower levels of dependent dilatation flow (DDF) in comparison with the 1st group by 3.5%, in the patients with the 2nd group by 4.4% (P<0.05), which indicates the depletion of the product nitric oxide due to an increase in vasoconstrictor factors. Reduced of induced dilation (EIVD), identical, but in a lesser extent. At patients of the 3rd group it decreased by 2,0 (P_1<0,05), at patients of the 4th group by 2,4% (P_2<0,05) in comparison to individuals with HPG without EAH.

In the patients of the 3rd and 4th groups are noted correlation communication between the level of EIVD and output diameter of HA(r = - 0,68, P<0,05 i r = - 0,70, P<0,01), and also the strong dependence is found between EDVD and ET-1 level (r = - 0,72, P<0,05).

The connection among during of diseases of CPH, COPD that is a cause and diameter of HA was studied. It is noted that the size of HA is more altered depending on the duration of COPD. The initial rate of blood flow in patients with CPH of the 1st and 2nd groups was 0.66 ± 0.005 m / s and 0.60 ± 0.002 m / s, the patients with CPH with high blood pressure - 0.54 ± 0.006 m / s (P<0.05) and 0.50 ± 0.003 m / s (P<0.05). The percentage increase in the rate of hyperemia also decreased in patients of the 3rd group by 6.6 ± 0.8% (P<0.05) and in patients of 4th group by 19.7 ± 1.0% (P<0.05).

Thus, summarizing the above data regarding the study of ED in patients with CPH in combination with EAH, it should be noted that ultrasound studies of HA indicators in combination with the level of nitric oxide, ET-1 indicate their significant role in the formation of CPH and more pronounced changes in ED in side of increasing factors of vasoconstruction and inhibition of formation of nitric oxide.

This contributes to the formation of HF, especially in patients with comorbid pathology, namely CPH with EAH. It should be noted, that EAH contributes significantly to the causing of hypertensive heart, so special attention is required to the study of the intracardiac hemodynamics of the right and left ventricle especially in the combination of CPH with EAH.

The research was revealed that patients with CPH combined with EAH even in the phase of compensation have significantly reduced CI and PI, a decrease in the rate of acceleration of blood flow through the aortic valve (P<0,05),

which led to a decrease in PV by 1.3 times (P<0,05) in compared to healthy persons, but it remained within the normal range (3rd group 50,0±2,5%). These changes indicate a additional contribution of the EAH to cause reduced systolic function on the period of hypoxia of toxic-infectious and metabolic effects of COPD. Even more pronounced were the changes revealed in patients with EAH of 4th group. All indicators (CI, PI, Vmax, size of LV) were significantly altered that confirms decrease of EF to 40,5±1,0%. Increasing hypertrophy of the posterior LV, especially of IVS, was also detected, but they did not reach the values that are characteristic of isolated EAH. The pathogenesis of these changes is explained by a decrease in inflow to the left heart due to increased total pulmonary resistance, pulmonary hypertension in the circulatory system and right ventricular failure.

The diastolic function of LV changed by relaxation type, it detected in 100% of patients. by relaxation type were also detected in 100% of patients. These changes were reflected in a decrease in the rate of early diastolic filling (E) to late (A) their ratio E/A, especially in patients with CPH in combination with EAH of 4th group, respectively by 0,3±0,001 m/s (P_2 <0,05) and 0,1±0,001 (P_1 <0,05) compared with the 2nd group of patients with CPH without EAH (P_1 <0,05) with increasing IVRT from 0,11±0,002s to 0,16±0,004s (P_2 <0,05). Significant thickening of the IVS is noted, which also plays a role in the formation of diastolic dysfunction of the LV. Violation of diastolic filling of the LV, along with changes in systolic function, was accompanied by its dilation by 7.6%.

Thus, the research showed that systolic dysfunction of LV heart is exacerbated by the adherence to essential hypertension in the CPH. pressure, decreased myocardial contractility on changes in LV, hypoxia, myocardial dystrophy, which are already present in COPD patients, are also important. Diastolic dysfunction of the LV heart appears already on the background of the formation of CPH in patients with COPD and is greatly exacerbated with EAH attachment and especially due to the development of HF.

CONCLUSIONS

1. The patients with bronchopulmonary genesis in combination with EAH are characterized by more pronounced changes in ED toward an increasing of the level of vasoconstrictor factors (ET-1), decreasing of vasodilators (metabolites of nitric oxide), which is naturally observed when joining arterial hypertension than in patients with isolated CPH and confirmed by ultrasound examination of the brachial artery, its high correlation with ED. This requires combination treatment to correct these changes and improve patients' prognosis.
2. The patients with CPH in combination with EAH as an indicators of metabolites NO, ET-1, ultrasonography of humeral artery indicate substantial contribution in progression endothelial dysfunction and circulatory insufficiency.
3. Changes in systolic and diastolic function of the LV the degree of which increases with the progressing of HF, combined pathology and correlates with the parameters of endothelial dysfunction (EF_{LV} – NO_2 - NO_3 r = 0,72, P<0,05; EF_{LV} – ET-1 r = 0,64, p<0,05) and deepened due to the development of decompensation.
4. Systolic dysfunction of the left ventricle is exacerbated when CPH joins to essential arterial hypertension. In addition, to the influence of high blood pressure, hypoxia, myocardial dystrophy, which are characteristic of patients with bronchopulmonary genesis are also important Diastolic dysfunction of the left ventricle of the heart appears already on the background of the formation of CPH and is greatly progressing in the combined pathology and especially, due to the progressing of EF, which is a predictive factor of aggravation.
5. The chronic pulmonary heart combined with essential arterial hypertension mutually exacerbate the disease in comparison with patients with isolated chronic pulmonary heart, indicating a syndrome of "mutual burden", which leads to a more severe course of the disease, that should be taken into account both in diagnosis and treatment.

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DISORDERS OF THE SKIN'S BARRIER FUNCTION IN PATIENTS WITH ATOPIC DERMATITIS WITH MUTATIONS OF THE FILAGGRIN GENE

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ABSTRACT

Introduction: The paper presents the results of investigations of the skin's barrier function in patients diagnosed with atopic dermatitis (AD) with the presence of one of the genetic predispositions, namely the filaggrin gene FLG 2284del4 mutation.

The aim: to deepen the study of the relationship between the mutations of the gene FLG del2282 and the morphological features of the skin, since the data on its physiological state in patients diagnosed with AD are contradictory that will contribute to the improvement of the modern basis necessary for the development of treatment-diagnostic and preventive measures.

Materials and methods: In the given study of patients diagnosed with AD (41 person), the frequency of the FLG 2282del4 gene deletion constituted 19.51% (8 patients) according to the method of Palmer *et al*. To determine the functional parameters of the skin in patients diagnosed with AD in the carriers of the FLG gene mutation and in patients void of this mutation, they have applied a multifunctional Aramo TS portable analyzer that enables to carry out dermatoscopic diagnosis of the skin surface.

Results and conclusions: As a result of the analysis of the obtained physiological parameters of the skin in the patients of both groups during the treatment process, it is noteworthy that the dynamics of these indices after treatment in patients void of the filaggrin gene mutation is significantly better in comparison with the patients in whom the filaggrin 2282 del14 gene mutation was revealed. There is a tendency towards the decrease of skin's moisture and elasticity in patients with revealed mutation compared with the ones who are void of it. Given this fact, the study of physiological parameters of the skin is important to consider when substantiating the diagnostic-treatment and prophylactic algorithm for patients diagnosed with AD.

KEY WORDS: atopic dermatitis, mutations in the filaggrin gene

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INTRODUCTION

One of the most common chronic recurrent skin diseases is known to be atopic dermatitis (AD). Atopic dermatitis is common throughout the world, in both sexes and in different age groups. Today, the prevalence of AD in the American infant population has reached 17.2%, in Europe 15.6%, and Japan 24%, reflecting a steady, more than three-fold, increase in the detection of AD compared to the 60s of the last century. The frequency of AD is significantly higher among the inhabitants of economically developed countries and is tending to continuous growth [1, 2].

Firstly, the hereditary predisposition has an important role in causing the disease (in particular, in barrier function violation). The genetic studies carried out have shown that in the first year of life, AD develops in 82% of children in case of allergy in both parents, in 59% of children if one of the parents was diagnosed with AD, and the other with allergic pathology of the respiratory tract, in 56% of children if allergy is observed only in one parent, in 42% of children if the first-line relatives show AD symptoms. But the onset of hereditary predisposition and clinical manifestations of atopy (atopic phenotype) occurs only through the action of the relevant factors of external conditions, proper for each individual [3, 4, 5].

The feature of AD, in contrast to other variants of atopic disease, is that the action of atopy mechanisms is aimed at the skin system and its functional properties, creating conditions for increasing its sensitivity to triggers of the environment [6, 7].

In recent years, intensive research has been conducted to study the structure, the function of the skin barrier, as well as therapies aimed at its recovery in case of AD and other chronic dermatosis [8, 9]. The reliability of the skin barrier, which protects the body from external factors, is an indispensable condition for survival [10, 11]. Its protective properties should remain stable and optimal, even under the external environment, which may suddenly change (for example, temperature, pH, relative humidity).

A special role in maintaining the normal condition of the skin surface and preventing the overdrying of the latter is performed by the horny layer. There is a delicate balance between the water content in the horn layer and the surrounding environment on the skin surface. To maintain the normal moisture of the stratum corneum, there exists a unique structure of desquamous corneocytes with highly specialized intercellular lipids that form a dense zone due to biliary layers located between corneocytes. This zone

directly performs the barrier function, regulating the perspiration, the loss of water, preventing the penetration of chemicals, and the intercellular space of the stratum corneum is considered to be an open system for the transfer of various substances in a concentration gradient (water, ions, gases). The exclusion of corneocytes contributes to the cleansing of skin from exogenous toxins, allergens and pathogenic microorganisms.

In recent years, intensive research has been conducted on the study of the structure and functions of the skin barrier, which plays a major role in protecting the body from the effects of external harmful factors. The results of the research convincingly prove that in the pathogenesis of AD, the damage to the epidermal barrier plays a significant role along with immune and genetic mechanisms [1, 12, 5].

The pathogenesis of AD has traditionally been understood to be associated with a genetic defect in the immune system, namely the development of «inside-outside», which leads to an anomaly of differentiating T-helper cells with antigenic action, activation of dependent cytokines (IL- 4, IL-5), hyperimmunoglobulinemia and eosinophilic reaction, the features of antigen-presenting Langerhans cells, an increase in the level of different IgG subclasses, a decrease of the level of γ-interferon (IFN-γ) [13, 11], then over the past 10 years in the world medical sources they actively discuss the new concept of AD pathogenesis, namely «outside-inside», based on the notion that the cause of the disease is not considered a genetic malfunction at the level of the immune mechanisms, but a differentiation violation of the epidermis granular cells due to the filaggrin gene mutation (FLG), a protein necessary for differentiation of the epidermis cells and the formation of a skin epithelial barrier [14].

Filaggrin is a protein whose synthesis occurs in cells of the granular layer, the main function of which is to maintain a balance between the humidity of the environment and the deep layers of the epidermis. Filaggrin is formed during the final differentiation of granular epidermis cells, when profilaggrin of keratogialine granules (mass 400 kD) is proteolytically cut into filaggrin molecules approximately weighing37 kD, consisting of 324 amino acids. Proteolytic enzymes disassemble filaggrin for amino acids, which become amino acids of the natural moisturizing factor. Using filaggrin, the binding and administration of keratin and other intermediate phylums into the keratinocytes cytoskeleton occurs, resulting in the formation of keratinized plates [1, 11, 14]. In the process of differentiation, the cell nucleus of the epidermal cells is decomposed, the cells themselves get flattened and the keratin molecules contained in the latter are aligned, creating the plates that are connected to the extracellular lipids. The lipoprotein layer of the horn cells replaces the cell membrane, forming an important impenetrable barrier, and provides the mechanical integrity of the skin. Thus, deficiency of filaggrin leads to a decrease in skin hydration, an increase in the pH level and an epidermal barrier, which is clinically manifested by the skin dryness (genetically linked xerosis).

In 2006, two zero mutations pR501X and c.2282del4 of the FLG gene in patients with vulgar ichthyosis (a hereditary disease associated with keratinization disturbances) were revealed in 15 families of Scottish, Irish and Americans of the European origin [15, 16]. In a more detailed study, attention was drawn to the fact that several members of families suffering from ichthyosis were also diagnosed with AD [16].

For the first time C.N. Palmer et al. [15] reported a decrease or absence of the FLG gene expression due to mutations associated with the loss of its functions, leading to an epidermal barrier and clinical manifestations of AD. To date, about 40 mutations of the FLG gene have been identified in European and Asian populations [17, 18, 15, 4, 16].

FLG is required to control the transepidermal water loss and to support hydration [17, 4], as well as for the cultivation and organization of the epidermis [15]. The FLG gene is located in the 1q21 chromosomal region of the epidermal differentiated complex (EDC). EDC is a massive cluster of genes covering the region of about 1.9 million pairs of nucleotides of human genomic DNA involved in the terminal differentiation of the epidermis and the formation of the stratum corneum [14, 18]. Certain EDC genes encode proteins associated with the formation of profilaggrin and trichohyalinum, as well as the family of S100A calcium-binding proteins [18]. Thus, EDC is a group of structurally and evolutionarily bound genes, with close interaction, a complicated mechanism for differentiating the epidermis, the violation of which leads to the AD development as well as other forms of chronic allergodermathosis [15].

While the FLG protein decomposes in the horny layer, several active compounds, namely glutamine, histidine, urea that play an important role in maintaining the homeostasis of the stratum corneum are formed. FLG is required to control the transepidermal water loss and to support hydration [1, 13, 14], as well as for cultivation and organization of the epidermis [19]. The FLG gene is located in 1q21chromosomal area in the epidermal differentiation complex composition (EDC). EDC is a massive cluster of genes surrounding the region of about 1.9 million pairs of nucleotides of human genomic DNA involved in the terminal differentiation of the epidermis and the formation of the stratum corneum [14, 18]. Certain EDC genes encode proteins associated with the formation of profilaggrin and trichohyalinum, as well as the family of S100A calcium-binding proteins [14]. Thus, EDC is a group of structurally and evolutionarily linked genes, with close interaction, a complex mechanism of epidermis differentiation, the violation of which leads to the development of AD and other forms of chronic allergodermathosis [16].

In addition, reducing the FLG gene expression decreases the level of «natural moisturizing factor» [12, 16]. Deficiency of FLG and / or products of its degradation contribute to the dry skin progression, which correlates with a clinical picture of the epidermal barrier violations with AD manifestation. Moreover, with a decrease in FLG, the «irritating» effect of allergens on dendritic cells increases,

while reducing the sensitivity threshold of the latter, which demonstrates the importance of this protein in the rearrangement of allergens penetration [20, 21].

Thus, in patients diagnosed with AD there is a complex of disorders that lead to dysfunction of the skin barrier, and its dehydration [7]. It should be noted that patients with AD may reveal a defect in the skin barrier, based on both genetic and acquired mechanisms. This defect can spoil he external factors such as scratches, the use of detergents, microbial colonization, as well as the effect of proteases of various allergens (in particular, proteases of home dust mites) [21].

Recognition of specific mechanisms involved in the pathogenesis of inflammatory diseases of the skin affected with AD will certainly contribute to the search and development of new, more effective methods of influencing the pathological process with a minimal amount of systemic effects [19].

The results of recent studies convincingly prove that in the pathogenesis of AD, psoriasis, eczema and a number of certain dermatoses, the damage to the epidermal barrier plays a significant role along with the immune mechanisms. Recently, methods of non-invasive skin diagnostics have been used in dermatological practice to evaluate both the physiological and morphological parameters of the skin [2, 13].

THE AIM

In this regard, an in-depth study of this multifactorial pathology, namely, the relationship between the mutations of the FLG del2282 gene and disorders with chronic dermatosis, in particular, the morphological features of the skin, is of relevance, as data on its physiological state in patients diagnosed with AD are not numerous and contradictory, which laid the basis for the given research that will make it possible to create a modern basis for the development of treatment/diagnostic and preventive measures.

MATERIALS AND METHODS

In the given study of patients diagnosed with AD (41 patients) who were admitted to hospital for inpatient treatment at the department of dermatology, infectious and parasitic diseases of the skin of the SU «IDV of the NAMSU», the frequency of the FLG 2282del4gene deletion constituted 19.51% (8 patients). The age range of patients covered the period from 20 to 70 years.

All patients were given a score assessment of the dermatosis severity through a SCORAD semi-quantitative scoring (Scoring Atopic Dermatitis) scale [8], which makes it possible to assess the extent of body lesions and the intensity of clinical manifestations combined with subjective symptoms, namely the intensity of itching (and as a consequence of this sleep disturbance). First of all, they carried out an assessment of objective symptoms, namely: hyperemia, dry skin, peeling, excoriation and lichenification. Each sign was evaluated from 0 to 3 points (0 is absence, 1 is light, 2 is medium, 3 is severe); itching and sleep disorders based on the average degree of their severity during the last 3 days / nights on a 10-point scale were characterized according to subjective criteria.

The SCORAD index was calculated using the following formula:

SCORAD = A / 5 + 7B / 2 + C,

where *A* is the affected skin area ,%;

B is the sum of marks of objective signs;

C is the sum of subjective attributes points.

All patients were submitted to general laboratory tests (blood, urine, biochemical parameters).

To determine the functional parameters of the patients' skin diagnosed with AD in the carriers of the FLG gene mutation and in patients void of this mutation, they applied Aramo TS multifunctional portable analyzer for carrying out dermatoscopic diagnosis of the skin surface. It made it possible to determine the following indices of the skin: humidity, elasticity and skin oiliness. Indicators such as humidity, elasticity, skin oiliness, smoothness and pigmentation were calculated by a device in standard units.

Functional parameters were determined on the areas of skin lesions before and after treatment. During the examination of patients, all sensors that fixed the data were perpendicular to the skin level, which the indices were taken from on the background of dry, clean skin surface without preparation by external therapy remedies.

Definition of the filaggrin gene mutations in patients diagnosed with AD was performed using a polymerase chain reaction. The determination of 2282del4 mutation was carried out by the method of Palmer *et al*. DNA required for study was obtained from peripheral blood samples, using the devices «GenPack» DNA PCR Test (produced in the Russian Federation). A fragment of the filaggrin gene containing the mutation was amplified using the primers RPT1P7/RPT2P1: 5`-AATAAGTCTGGACACTCAGGT-3` and 5`-GAGGACTCAGACTGTTT-3`. The reaction results were determined using a transyluminator after electrophoresis of specimens in a 2% agarose gel simultaneously with standard markers of the molecular weight SM0373 (50-1000 np) produced by ThermoScientific company (USA).

RESULTS

For a more detailed study of the factors that lead to epidermal barrier violations, in patients diagnosed with AD, analysis of the skin functional parameters, taking into account the effect of the filaggrin gene mutation (FLG) –2282del4 on the respective data and the progress of the disease, was performed.

In the study of patients diagnosed with AD (41 person), the frequency of the FLG 2282del4 gene deletion constituted 19.51% (8 patients).

In the course of the studies, seasonality was noted in 85% of patients (35 patients out of 41). At the same time, a stable remission in the summer months and exacerbation in the autumn-winter-spring time was typical for them. In 15%

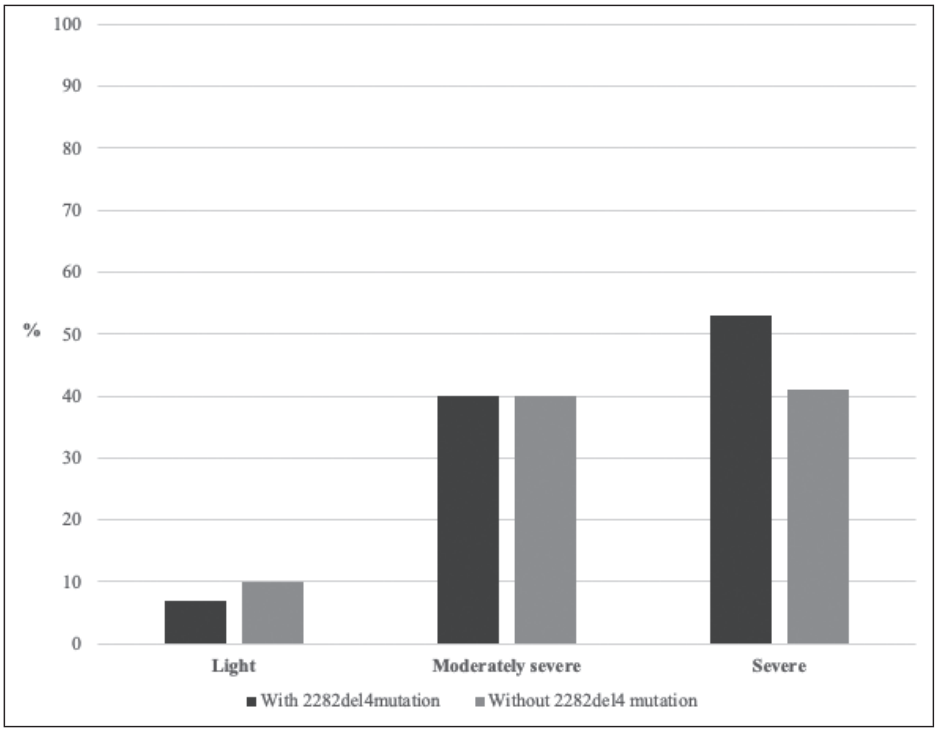

Figure 1. Degree of severity of AD in patients with FLG mutation.

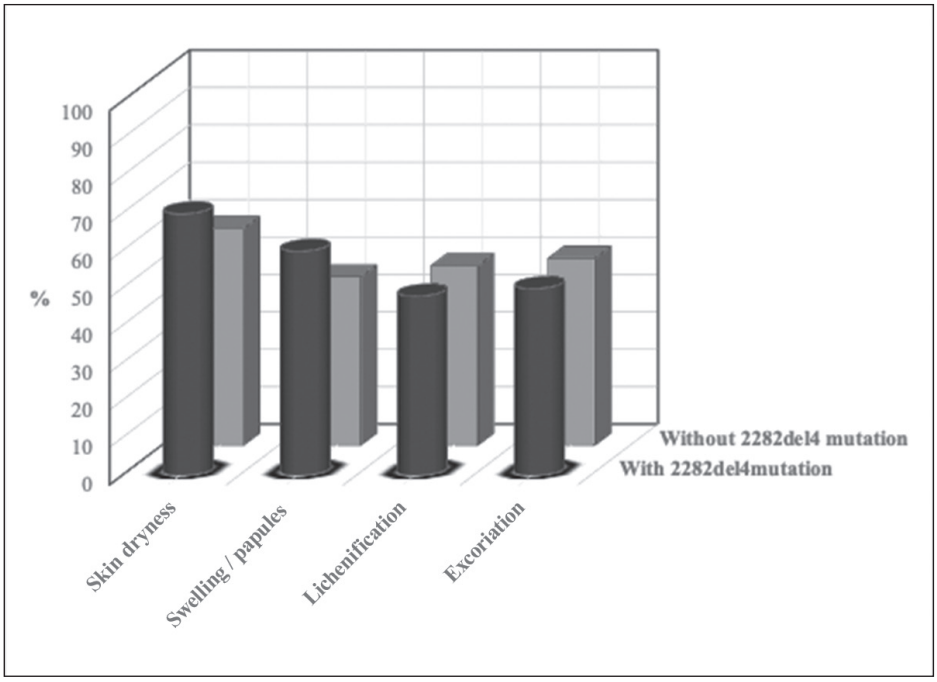

Figure 2. Estimation of objective clinical symptoms of AD in patients with FLG mutation and without mutation at the time of the survey.

of patients, the disease progression appeared to be without remission periods and was characterized by a continuously recurrent disease progression. In the in-depth analysis of anamnestic data, they identified several groups of factors which most often played a provocative role in the occurrence of relapses and disease exacerbations. These included psychoemotional factors, medicines, chemical products, physical activity, the effect of allergens (atopens), changes in meteorological conditions, as well as exacerbation of chronic infections, the presence of colds and stress, as well as neuro-conflict situations, psycho-emotional and mental strain (18%)

In determining the condition of skin lesions using the SCORAD index, a mild case was revealed in 3 patients (7.3%, from 12 to 19.8 points). The clinical features of these patients were characterized by moderate, often local, itching and slight lichenification. The absence of pathological changes in laboratory tests of peripheral blood (physiologically normal amount of leukocytes, eosinophils, etc.) was noted.

Table. 1. Evaluation of physiological parameters of skin in patients without / with mutation of filaggrin gene before and after treatment

Signs of the skin	Patients (Group 1)		Patients with philaggrin gene mutations (Group 2)	
	Before treatment,%	After treatment,%	Before treatment,%	After treatment,%
Humidity	46,7	67,9	44,6	55,17
Elasticity	44,57	49,7	43,17	45,89
Oily skin	41,2	44.21	32	33
Smoothness	24,65	34,21	24,42	30
Pigmentation	52,43	45	53,42	49

In 18 patients (43.9%) they observed a moderately severe manifestation of the disease (the average rate ranged from 20.2 to 39.5 points), the degree of the pathological process activity, in these patients, was characterized by severe itching, more widespread skin lesions, increased lichenification, appearance of excoriations, pruri-ginous papules, increased acuity of the inflammatory process, microbial lesions were joined, and deviations of laboratory parameters were revealed.

In 21 patients (51.2%), the disease progressed in a severe form (with extreme fluctuations from 42.3 to 76 points). There were observed widespread lesions of the skin, often of a gastrointestinal nature. In the disease-bearing areas, there were observed numerical papular elements of red color, with the merging of which cells of a holistic papular infiltration and massive skin lichenification were formed. Often, in the affected areas, there were noticed numerous significant extirpations and pruriginous papules on the background of swollenness, as well as a significant number of scales. The proportion of patients with skin lesions was generalized in the form of total erythroderma.

Almost all patients had extreme skin dryness accompanied with a massive finely-laminae peeling. Almost all patients complained of intense burning itching, which led to sleep disorders and mental exhaustion. Patients had frequent attachment of bacterial secondary infection, which oftimes increased the disease severity.

In subgroups of patients with FLG 2282del4 mutation or without it, assessment of the AD severity degree did not statistically reveal significant differences. In each of them, the average degree of disease severity prevails, but it should be noted that patients with 2282del4 mutation 3 times more were likely to have severe cases compared with patients void of the given mutation (Fig. 1).

Thus, the data presented coincide with the literature data, in which there was not revealed clear correlation of the FLG 2282del4 gene mutation accompanied with the severity of the disease [4, 16] progression.

At the time of the study, most patients were in the stage of disease exacerbation. The SCORAD index in patients with FLG mutation was in the range of 38.08 to 70.4 points, while in patients without 2282del4 mutation it was in the range of 40.5 to 73.5 points.

Analysis of objective clinical symptoms of AD in patients is presented in Figure 2. Among the patients under medical supervision, the main objective symptoms of AD appeared to be dry skin and lichenification. Also, swelling / papules and erythema were observed; however, none of the objective symptoms of AD as well as their score were statistically significantly different in the comparison subgroups.

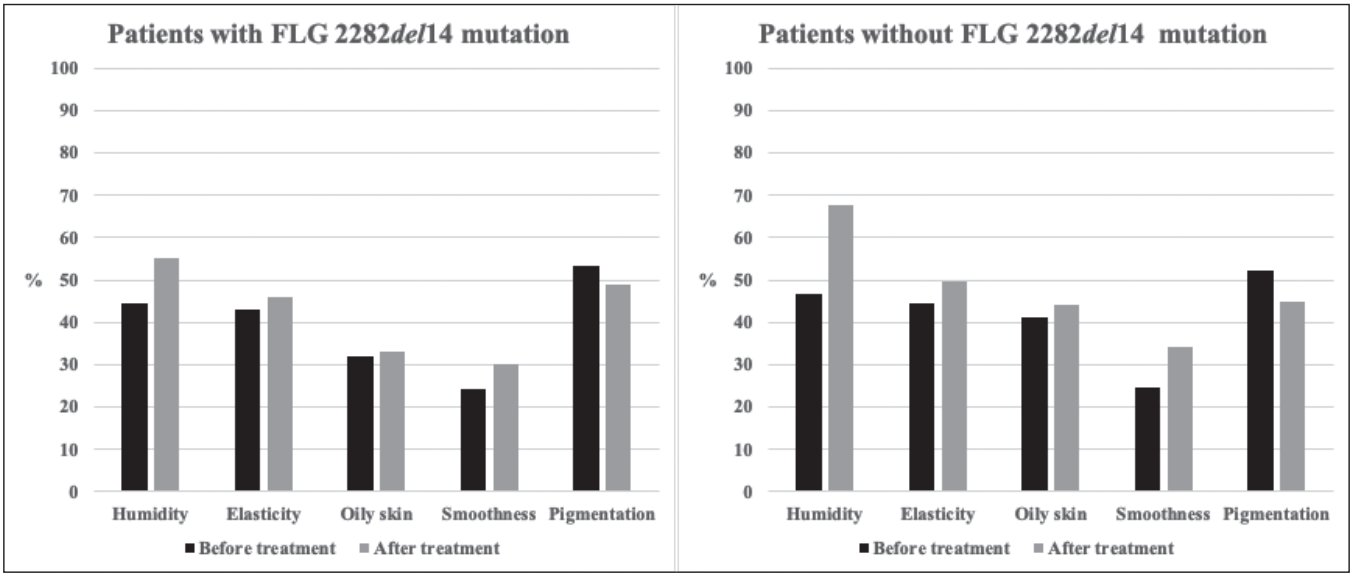

Figure 3. Dynamics of changes in physiological parameters of the skin in patients before and after treatment.

In connection with violations of the epidermal skin barrier, all patients underwent tests of the physiological skin parameters before and after treatment. The following indicators were evaluated: humidity, elasticity, oily deposits, smoothness, pores and pigmentation (Tab I, Fig. 3).

As a result of analysis of the results of the physiological skin parameters in patients of both groups, the attention is drawn to the decrease of the skin moisture, the tendency to reduce elasticity and increase pigmentation in patients of both groups before treatment.

As a result of analysis of the obtained indices of the physiological parameters of the skin in patients of both groups during the treatment process, it is noteworthy that the dynamics of these indices after treatment in patients without the filaggrin gene mutation is significantly better in comparison with those diagnosed with the mutation of the filaggrin 2282 del14gene.

CONCLUSIONS

Thus, the data presented coincide with the literature data, in which there was no clear relationship between the mutations of the FLG 2282del4 gene and the disease severity. As a result of the analysis of obtained indices of the physiological parameters of the skin in patients of both groups, the attention is drawn to the decrease in the index of skin moisture, the tendency to reduce elasticity and increase pigmentation in patients of both groups before treatment. However, the dynamics of these indices after treatment in patients void of the filaggrin gene mutagenesis is significantly better than in those diagnosed with the mutation of filaggrin 2282 del4. This fact must be taken into account when substantiating the diagnostic-treatment and prophylactic algorithm for patients with chronic dermatosis.

As a result of the research, it was established:

- there was no clear relationship between the mutation of the FLG 2282del4 gene and the severity of the atopic dermatitis progression;
- Itching was diagnosed in patients of both groups (with mutation of the filaggrin gene and without mutation), but in patients with filaggrin gene mutation itching is observed not only on the affected but also on the intact parts of the skin;
- As a result of the analysis of the obtained indices of the physiological parameters of the skin in patients of both groups, there is a decrease in the index of skin moisture, a tendency to reduce elasticity and increase pigmentation in patients of both groups prior to treatment;
- The dynamics of skin moisture index, the tendency to decrease elasticity and increase pigmentation after treatment in patients without filaggrin gene mutagenesis is significantly better than in those diagnosed with filaggrin 2282del4 mutation;
- the revealed features should be taken into account when substantiating the diagnostics/treatment and preventive algorithm for providing patients diagnosed with chronic dermatosis with proper medication.

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ORIGINAL ARTICLE
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DENSITY AND MINERAL CONTENT DYNAMICS OF BONE TISSUE OF THE LOWER JAW OF THE RAT ON THE BACKGROUND OF OPIOID INFLUENCE AND AFTER ITS WITHDRAWAL

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ABSTRACT

Introduction: Over the past few years, the use of pharmaceuticals by the population, in particular, analgesics, has become widespread, and often their use is unreasonable from the medical point of view and leads to structural and functional changes in organs and systems of the body and to the development of drug dependence.

The aim of our work was to study the qualitative changes and dynamics of the mineral content of rat bone tissue under prolonged opioid exposure.

Materials and methods: The study was performed on 40 sexually mature male rats with a body weight of 180-200 g and 3.5 months old. Opioid dependence was modeled by the daily (once a day at the same time interval) injection of a narcotic analgetic Nalbuphine.

Results and conclusions: The study showed that the density and mineral content of the bone tissue of the rat's mandible on the background of 6 weeks opioid action of nalbuphine and after its withdrawal have a pronounced dynamics, different and characteristic for each of the investigated parameters. The results of the atomic absorption spectral analysis of the bone tissue of the rat's mandible body allow the determination of the quantitative content of four macro-elements (Ca, P, Mg, Na) and four microelements (K, Fe, Sr, Zn) and investigate their dynamics during the experiment. On the background of the nalbuphine use absolute indices of calcium, phosphorus, magnesium, sodium, zinc and iron content increase, remaining above the norm after its withdrawal; the amount of potassium decreases and remains lower than norm and after the withdrawal of nalbuphine, and the amount of strontium is also reduced, but minimal, and after the withdrawal of nalbuphine has the same value as in intact animals.

KEY WORDS: mandible, mineral content, nalbuphine, opioid dependence

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INTRODUCTION

Over the past few years, the use of pharmaceuticals by the population, in particular - analgesics, has become widespread, and often their use is unreasonable from the medical point of view [1-6]. Numerous clinical observations and experimental studies suggest that prolonged use of drugs that suppress pain leads to structural and functional changes in body organs and systems, and the development of drug addiction [1, 7-10]. That is why a deep and versatile study of the influence of medications of this group on the body is very important today.

The results of numerous studies show that long-term use of opioids can accumulate in the body and cause significant changes in the function of various structures and areas of the brain, kidneys, pancreas, myocardium, lymphoid organs, eyeball, tongue, skin, etc., as well as in the behavior of experimental animals [11-19]. However, information on the influence of opioids on bone tissue in scientific medical literature is practically absent today.

THE AIM

The purpose of our work was to study the qualitative changes and dynamics of the mineral content of rat bone tissue with prolonged exposure to the opioid.

MATERIALS AND METHODS

The study was performed on 40 sexually mature male rats with a body weight of 180-200 g and 3.5 months old. Experimental animals were kept in the vivarium of the Danylo Halytsky Lviv National Medical University. All studies were conducted in accordance with the provisions of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (Strasbourg, 1986), Council of Europe Directive 86/609 / EEC (1986), Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruel handling".

Opioid dependence was modeled by the daily (once a day at the same time interval) injection of a narcotic analgetic of nalbuphine. Nalbuphine was injected intramuscularly according to the following schedule: 1 week - 8 mg / kg, 2nd week - 15 mg / kg, 3rd week - 20 mg / kg, 4th week - 25 mg / kg, 5 -this week - 30 mg / kg, 6th week - 35 mg / kg [20].

Control of the quality of bone tissue of the alveolar part of the mandible was performed using the Dental radiosignographer Siemens with the Trophy Radiology software. The unit of measurement of tissue density was the conventional unit of gravity (CUG).

To determine the mineral composition of the bone tissue of the rat's mandible, the method of atomic absorption spectral analysis (AASA) was used, which allowed to detect the contents of eight mineral elements in the studied samples

Table I. Density of the bone tissue of the rat's mandible during six weeks of nalbuphine use and after its withdrawal (CUG)

Experimental groups	M	Dyspersion	Δ	M-Δ	M+Δ
Norm (intact animals)	75,33	177,87	14,00	61,34	89,33
1st week	78,17	191,77	14,53	63,63	92,70
2nd week	85,67	809,47	29,86	55,81	115,52
3rd week	75,50	333,10	19,15	56,35	94,65
4th week	82,33	433,07	21,84	60,49	104,17
5th week	83,17	380,97	20,48	62,68	103,65
6th week	79,50	537,50	24,33	55,17	103,83
1 week after Nalbuphine withdraw	79,50	420,70	21,52	57,98	101,02

Table II. Content of mineral elements in the bone tissue of the rat's mandible during six weeks of nalbuphine use and after its withdrawal (mg/g)

		Ca	P	Mg	Na	K	Zn	Fe	Sr
control	M	14,0067	11,5633	2,7867	2,4333	2,9533	0,1567	0,4500	0,2000
	M-Δ	13,7925	10,2827	2,2525	2,0539	2,8413	0,0942	0,3258	0,0758
	M+Δ	14,2208	12,8438	3,3208	2,8128	3,0653	0,2192	0,5742	0,3242
1 week of experiment	M	58,2333	12,8833	3,6233	3,1500	1,2467	0,2700	0,6300	0,2000
	M-Δ	57,3609	11,5133	3,4241	3,1003	1,2087	0,2452	0,5058	0,0758
	M+Δ	59,1057	14,2532	3,8226	3,1997	1,2846	0,2948	0,7542	0,3242
2 week of experiment	M	48,8500	11,7566	3,5200	3,3300	1,6700	0,4500	1,4467	0,2000
	M-Δ	48,6016	11,6198	3,3461	3,2803	1,6203	0,4252	1,3216	0,0758
	M+Δ	49,0984	11,8934	3,6939	3,3797	1,7197	0,4748	1,5717	0,3242
3 week of experiment	M	50,3800	12,2900	3,4833	3,1000	1,1200	0,3033	0,6767	0,1900
	M-Δ	44,4926	11,1224	3,2969	3,0503	1,0703	0,2654	0,5399	0,0658
	M+Δ	56,2674	13,4575	3,6698	3,1497	1,1697	0,3413	0,8135	0,3142
4 week of experiment	M	56,5800	12,5666	2,9433	3,3433	0,5600	0,2700	1,7267	0,1767
	M-Δ	54,9849	11,6252	2,7072	3,2808	0,9467	0,2203	1,5769	0,0647
	M+Δ	58,1751	13,5081	3,1794	3,4058	2,0667	0,3197	1,8764	0,2887
5 week of experiment	M	48,6500	12,9466	3,9800	2,9300	1,5833	0,3600	1,2567	0,2000
	M-Δ	48,5258	12,8462	3,6542	2,2789	1,4465	0,3352	1,1447	0,0758
	M+Δ	48,7742	13,0470	4,3058	3,5811	1,7201	0,3848	1,3687	0,3242
6 week of experiment	M	52,7500	14,8466	4,4367	3,6600	1,3000	0,2600	1,2300	0,1900
	M-Δ	51,3092	14,6850	4,2254	2,8387	1,2255	0,2352	1,0917	0,0658
	M+Δ	54,1908	15,0082	4,6479	4,4813	1,3745	0,2848	1,3683	0,3142
7 week of experiment	M	44,3733	12,5900	3,0467	2,7333	1,4933	0,3267	1,2333	0,2000
	M-Δ	41,9508	11,1962	2,1221	2,4208	1,2324	0,2887	1,0965	0,0758
	M+Δ	46,7959	13,9837	3,9713	3,0459	1,7543	0,3646	1,3701	0,3242

(of which four macroelements: calcium (Ca), phosphorus (P), magnesium (Mg), sodium (Na) and four microelements: potassium (K), iron (Fe), strontium (Sr), zinc (Zn)). Concentration of the investigated elements in bone tissue samples was indicated in mg/g. Studies of the quality and mineral content of the mandibular bone were performed weekly for 7 weeks of the experiment - 6 weeks of use of nalbuphine and one week after its withdrawal (5 animals per experiment period); 5 other animals were in the control group.

The obtained results were processed using mathematical statistics methods. For each parameter, the arithmetic mean value, dispersion and confidence interval were determined at a confidence level of P = 95%.

RESULTS AND DISCUSSION

The conducted study showed the presence of expressed dynamics of bone tissue quality of the mandible during the seven weeks of the experiment (Table I).

Analysis of the dynamics of the studied parameter in experimental groups shows that after two weeks of nalbuphine use, the density of bone tissue of the mandible gradually

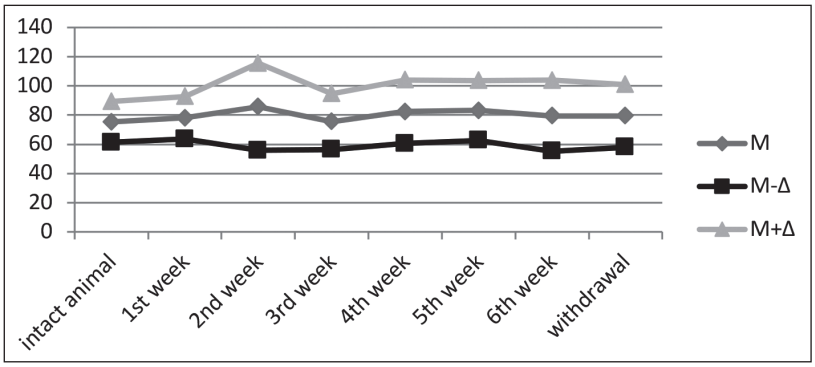

Fig. 1. Dynamics of density of bone tissue of rat's mandible during 6 weeks of nalbuphine use and after its withdrawal.

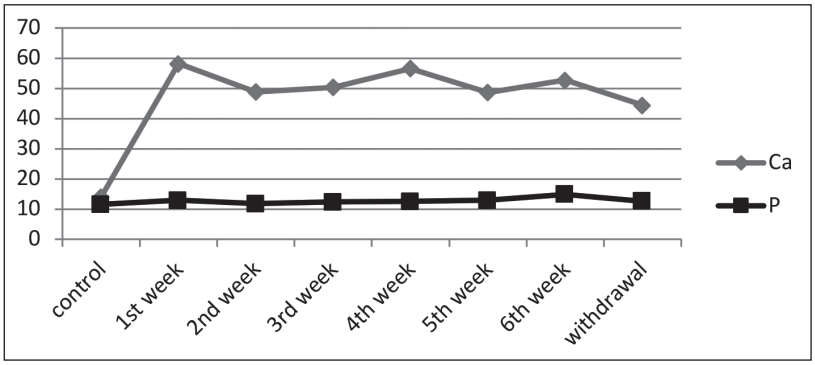

Fig. 2. Dynamics of the content of calcium and phosphorus in the bone tissue of the body of the mandible of the rat during the six weeks of opioid exposure and after its withdrawal.

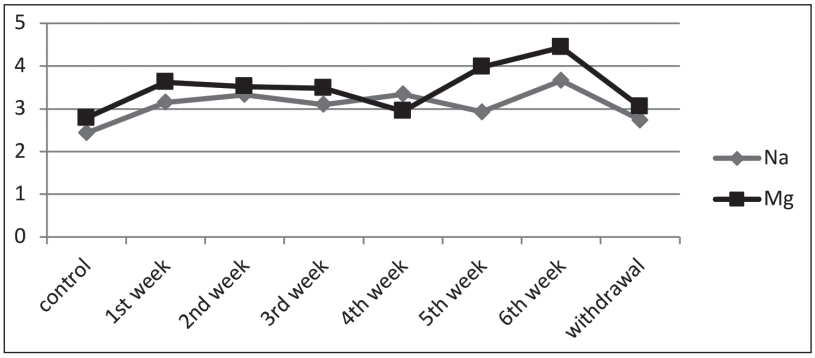

Fig. 3. Dynamics of the content of sodium and magnesium in the bone tissue of the body of the mandible of the rat during the six weeks of opioid exposure and after its withdrawal.

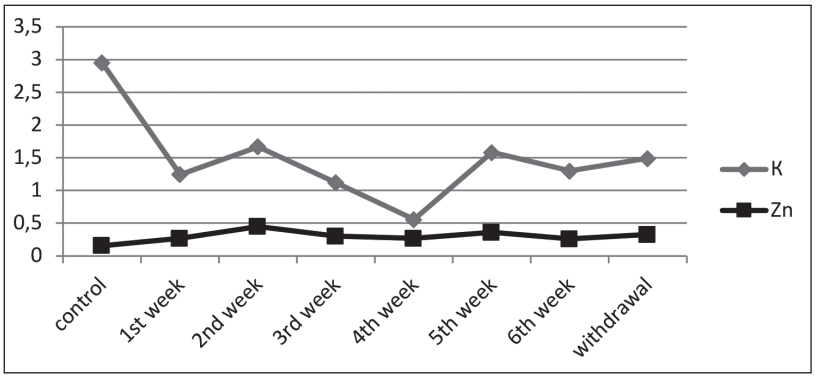

Fig. 4. Dynamics of potassium and zinc content in the bone tissue of the rat's mandible body during the six weeks of opioid exposure and after its withdrawal.

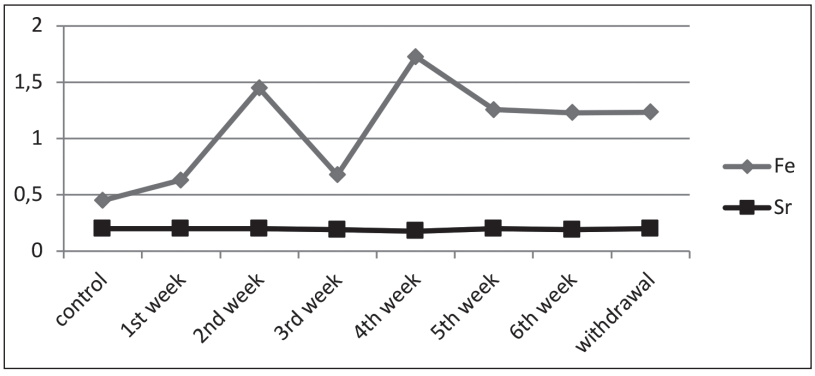

Fig. 5. Dynamics of iron content and strontium in the bone tissue of the rat's mandible body during the six weeks of opioid exposure and after its withdrawal.

increases in comparison with control group, and during the third week it decreases, returning, to almost normal values. During the fourth and fifth weeks, the researched parameter is rising again, and in the sixth week it decreases and remains unchanged for one week after withdrawal of the drug, but somewhat higher than in intact animals (Fig. 1).

The analysis of the mineral content of the bone tissue of the rat mandible body in norm, as well as during six weeks of nalbuphine use and after its withdrawal, allowed to determine the quantitative content of all investigated elements in the bone tissue at each stage of the experiment and showed the presence of their expressed dynamics (Table II, Figure 2-5).

The study of the dynamics of the mineral composition of the bone tissue of the rat's mandible body during six weeks of nalbuphine use and a week after its withdrawal made it possible to find out that the absolute indexes of the content of the studied macro- and microelements (Fig. 2- 5).

The content of calcium in the bone tissue of the body of the mandible increases significantly in a week from the beginning of the experiment, reaching the maximum value and exceeding the norm four times (58,2333 + 0,1242 mg/g). During the six weeks of the experiment, the calcium content is 3-4 times higher than that of intact animals, and after nalbuphine withdrawal exceeds the norm in three times (44,3733 + 0,1368 mg / g) (Table II, Figure 2).

The amount of phosphorus changes slightly during the experiment, reaching the maximum value at the sixth week of using nalbuphine (14,8466 + 1,6163 mg/g) and decreasing after its withdrawal (12,5900 + 13,9378 mg/g), but remains higher than in intact animals (Table II, Figure 2).

The amount of magnesium and sodium in the bone tissue of the mandible also increases with the nalbuphine use, but the dynamics of their content is unstable. The maximum amount of magnesium and sodium reaches the sixth week of the experiment (4,4367 + 1,4408 mg / g and 3,6600 + 0,2113 mg / g respectively), and after its withdrawal decreases, remaining slightly higher than in the control group (3,0467 + 2,4226 mg/g of magnesium and 2.7333 + 0.9246 mg/g of sodium) (Table II, Figure 3).

During the first week of nalbuphine use, potassium content is reduced by more than twice as compared with intact animals (1.2467 + 0.0248 mg/g), and the minimum index (0.5600 + 0.0497 mg/g) reaches the fourth week of the experiment. After the nalbuphine withdrawal, the amount of potassium in the bone tissue of the investigated area remains twice lower than the norm (1.4933 + 0.0379 mg / g) (Table II, Figure 4).

The amount of zinc in the bone tissue on the background of the nalbuphine use increases, reaching the highest value in the second week of the experiment (0,4500 + 0,0497 mg/g), and after nalbuphine withdrawal remains twice higher (0,3267 + 0,2609 mg/g) (Table II, Figure 4)

The content of iron in bone tissue during the six weeks of the experiment is higher than in the norm, the maximum (1,7267 + 0,0625 mg/g), which exceeds the norm by almost four times, reaches four weeks of use of nalbuphine, and after it the withdrawal remains three times higher than in intact animals (1,2333 + 0,3126 mg / g) (Table II, Fig. 5).

The amount of strontium with the use of nalbuphine remains the most stable among the studied macro- and microelements, slightly decreasing only during the third, fourth and sixth weeks of the experiment. The minimum value (0,1767 + 0,1120 mg / g) of the content of strontium in the bone tissue reaches the fourth week of the nalbuphine use, and after its withdrawal, the amount of the test element in the bone tissue is the same as in intact animals (0,2000+ 0,1242 mg / g) (Table II, Figure 5).

The results of the studies have made it possible to determine the course of qualitative changes and dynamics of the mineral composition of the bone tissue of the mandible of the rat on the background of long-term opioid exposure. Further study of these processes will allow to search and develop ways of their correction for people who have been taking opioid group drugs for a long time.

CONCLUSIONS

The analysis of dynamics of density of bone tissue of the mandible and its mineral composition during the 7-week experimental period led to the following conclusions:

1. Density and mineral content of the bone tissue of the rat's mandible on the background of 6 weeks of use of the drug opioid action of nalbuphine and after its withdrawal have expressed dynamics, different and characteristic for each of the studied parameters.
2. During two weeks of using naluphenine, the density of mandibular bone tissue gradually increases until the end of the second week of the experiment, reaching its maximum value, decreases sharply in the third week, increases slightly over the next two weeks and changes minimal to the end of the experiment, staying above the norm and after withdrawal of the drug.
3. The results of the atomic absorption spectral analysis of the bone tissue of the rat's mandible body allow to determine the quantitative content of four macroelements (Ca, P, Mg, Na) and four microelements (K, Fe, Sr, Zn) and to investigate their dynamics during the experiment
4. On the background of the nalbuphine use, absolute values of calcium, phosphorus, magnesium, sodium, zinc and iron increase, remaining above the norm and after its withdrawal; the amount of potassium decreases and remains lower than norm and after the nalbuphine withdrawal, and the amount of strontium is also reduced, but minimal, and after the nalbuphine withdrawal has the same value as in intact animals.

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ANALYSIS OF EXPRESSION OF P63 AND CASPASE-3 AND THEIR PREDICTIVE VALUE IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF MAXILLARY SINUS

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ABSTRACT

Introduction: Maxillary sinus cancer is a malignant neoplasm with a prevalence of 3 to 5% of tumors in the head and neck and less than 1% of all malignant neoplasms. The role of p63 and caspase-3 and their predictive value in squamous cell carcinoma of maxillary sinus (SCCMS) remains an underdeveloped and controversial issue that determined the relevance of the study.

The aim: To analyze the relationship between the level of expression of p63 and caspase-3 and clinical and morphological characteristics of squamous cell carcinoma of maxillary sinus and to determine their prognostic significance as immunohistochemical markers of tumor progression (relapse and metastases).

Materials and methods: A comprehensive investigation with immunohistochemical study of squamous cell carcinoma of maxillary sinus of 103 patients with maxillary sinus cancer II - IV stage (T2-4 N0-3 M0) of the second clinical group was conducted.

Results: The moderate and high expression rate of caspase-3 in the overall sample was 50.49% and 16.50% respectively, and one third of cases (33.01%) was characterized by a weak reaction. In the group without metastases ($p < 0.001$), moderate expression of the marker (56.25%) prevailed; in the SCCMS group with metastases it was (60.87%). The mean level of expression of p63 in the examined patients with squamous cell carcinoma of maxillary sinus was 46.0%. The number of p63-positive specimens was statistically significantly ($p = 0.034$) higher in the SCCMS group with metastases.

In patients with the development of squamous cell carcinoma of maxilla on the background of papilloma, a significantly higher ($p < 0.001$) mean level of p63 expression was only moderate (90.91%) and high (9.09%).

Conclusions: There was observed a relatively strong associate of the increase in the expression of caspase-3 with SCCMS metastases ($p < 0.001$) and no correlation of immunohistochemical reaction of this marker with relapses.

There was determined that the probability of metastases at high expression level of p63 is higher than in tumors with low and moderate level of the oncoprotein ($p = 0.003$). Based on the level of expression of p63, it is possible to predict the likelihood of development of SCCMS with papillomas ($p < 0.001$); and the development of relapses of squamous cell carcinoma of maxillary sinus ($p < 0.001$).

KEY WORDS: squamous cell carcinoma of maxillary sinus, marker p63, caspase-3

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INTRODUCTION

Maxillary sinus cancer (MSC) is a malignant neoplasm with the prevalence of tumors in the head and neck - from 3 to 5%, and of all malignant neoplasms less than 1%. Patients have low survival rate and high disability due to nonspecific symptoms, late referring to a doctor, complications after surgical interventions and predisposition for relapse and metastases [1,2]. Of maxillary neoplasms, squamous cell carcinoma (SCC) occurs most commonly, accounting for 80% - 90% of head and neck cancer, and 60-75% of malignant tumors of paranasal sinuses [3].

Biomolecular markers of tumors allow to diagnose neoplasms, determine the degree of risk, as well as to predict the course and evaluate the effectiveness of treatment. They are conventionally divided into two groups: markers used for diagnosis and cell differentiation and biomolecular markers that determine the potential of tumor malignancy (proliferation, apoptosis, invasive growth and metastases) [4].

The first group of immunohistochemical markers includes oncoprotein p63, the second group of tumor progression markers - caspase-3.

Investigations of many scientists point at the increase in expression of p63 gene in neoplasms, due to this fact the hypothesis that it functions as a natural inhibitor of p53, suppressing its function by the dominant-negative mechanism became up-to-date. [5].

It has been determined that excessive expression of p63 is observed in many squamous cell carcinomas, indicating that this oncoprotein can act as an oncogene [6].

High levels of protein p63 are characteristic of malignant cells of various localizations - skin epithelium, esophagus, tonsils, cyst, prostate gland, mammary gland, bronchi. The role of p63 in squamous cell and transient cell carcinomas, as well as some lymphomas and thymomas has been confirmed [7].

Various p63 isoforms play different roles in tumor progression. In the series of studies it has been shown that

Table I. Indices of caspase-3 expression in the examined patients with squamous cell carcinoma of maxillary sinus.

Indices	Expression of caspase-3			Differences and relationships between groups
	Weak	Moderate	High	
All examined (n=103)	34 (33,01)	52 (50,49)	17 (16,50)	-
Metastases of SCCMS, n (% of total number)				
SCCMS without metastases (n=80)	32 (40,0)	45 (56,25)	3 (3,75)	p<0,001* V=0,65 ρ=0,51 (p<0,001)
SCCMS with metastases (n=23)	2 (8,7)	7 (30,43)	14 (60,87)	
Relapse of SCCMS, n (% of total number)				
Without relapse (n=91)	32 (35,16)	45 (49,45)	14 (15,38)	p=0,395* V=0,13 ρ=0,13 (p=0,179)
With relapse (n=12)	2 (16,67)	7 (58,33)	3 (25,0)	
Morphologic variant of tumor, n (% of total number)				
Typical SCC (n=91)	30 (32,97)	49 (53,85)	12 (13,19)	p=0,031* V=0,26 ρ=-0,11 (p=0,250)
Atypical forms (n=12)	4 (33,33)	3 (25,0)	5 (41,67)	
Degree of histologic differentiation of tumor, n (% of total number)				
Low (n=38)	8 (21,05)	17 (44,74)	13 (34,21)	p=0,001* V=0,29 ρ=-0,22 (p=0,020)
Moderate (n=52)	18 (34,62)	30 (57,69)	4 (7,69)	
High (n=13)	8 (61,54)	5 (38,46)	0 (0)	
Keratinization of tumor, n (% of total number)				
Non-keratinized SCC (n=62)	26 (41,94)	27 (43,55)	9 (14,52)	p=0,060* V=0,23 ρ=0,21 (p=0,038)
Keratinized SCC (n=41)	8 (19,51)	25 (60,98)	8 (19,51)	

Note. * - differences between the groups according to Pearson's χ2 criterion; associations between the groups according to Cramer's V-criterion (Cramer's V) and Spearman correlation coefficient (ρ)

p63 is involved in apoptotic signaling, but its role in this process remains controversial [8].

Apoptosis depends on the proper activation of caspases, caspase-3 in particular, which leads to the splitting of key proteins such as PARP-1. Resistance to apoptosis, detected by caspases determination, highlights resistance to therapy given and poor prognosis for patients [9]. Inhibition of caspase-3 activity may be beneficial biochemical target for the development of chemotherapeutic drugs for cancer treatment [10].

For SCC of the oral cavity higher levels of expression of caspase-3 are associated with less relapse-free survival of patients with moderate cell differentiation and small tumor size, while at the same time a better survival of patients in later stages of the disease, with a large tumor size and lymph node invasion is observed [11]. In low correlation of expression of caspase-3 with prognosis for patients, caspase-3 activation is the most important process of apoptosis induction [12].

Despite the fact that many authors actively explore the peculiarities of expression of biomolecular markers in the cells of malignant tumors [13, 2, 4, 14], the role of p63 and caspase-3 and their predictive value for squamous cell carcinoma of maxillary sinus remains poorly developed and controversial issue, which conditioned the relevance of the study.

THE AIM

To analyze the relationship between the level of expression of p63 and caspase-3 and clinical and morphological characteristics of squamous cell carcinoma of maxillary sinus and to determine their prognostic significance as immunohistochemical markers of tumor progression (relapse and metastasis).

MATERIALS AND METHODS

There was conducted a comprehensive clinical and morphological research with pathohistological and immunohistochemical study of biopsy material of squamous cell carcinoma of maxillary sinus of 103 patients with cancer of maxillary sinus II-IV stages (T2-4 N0-3 M0) of the second clinical group, who were on inpatient treatment in the ENT-oncology department of the Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov over the period from 2011 to 2016.

Distribution to groups depending on the presence of metastases was as follows: group with squamous cell carcinoma of maxillary sinus without metastases - 80 patients (77.67%), group with metastases - 23 patients (22.23%). According to statistics, there were 66 male patients (64,08%), of them 54 patients (67,5%) - without

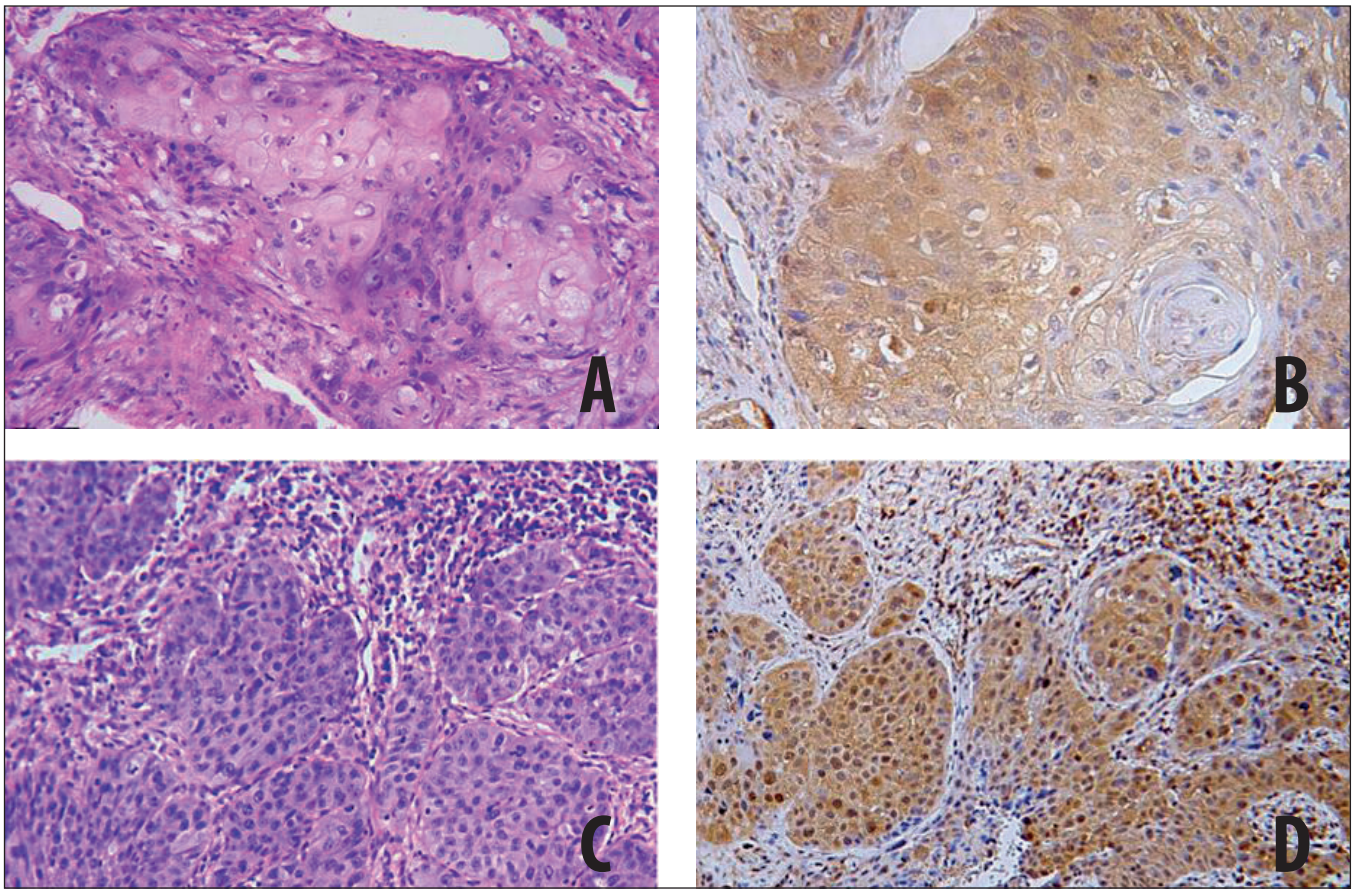


Fig. 1. A. Keratotic highly differentiated SCCMS, staining with hematoxylin-eosin (× 400). B. Keratotic SCCMS, moderate reaction of cells around «cancer pearls» (++) with caspase-3, IHM method, additional staining with Mayer's hematoxylin (× 400). C. Non-keratitic moderately differentiated SCCMS, staining with hematoxylin-eosin (× 400). D. Non-keratitic SCCMS, moderate reaction (++) with caspase-3 of tumor cells and strong (+++) in inflammatory infiltrating cells, IHM method, additional staining with Meyer's hematoxylin (× 400).

metastases, 12 patients (52.17%) - with metastases. Among 37 females patients (35.92%), 26 (32.5%) there were patients without metastases, 11 patients (47.83%) - with metastases (p = 0.177). Age up to 45 years - 18 patients (17.48%), 13 patients (16.75%) - without metastases, 5 patients (21.74%) - with metastases; those of aged 45 - 65 years - 65 patients (63.11%), 52 patients (52.0%) - without metastases, 5 patients (21.74%) - with metastases. The overwhelming majority in both groups (p> 0,05) were 65 years of age and 20 patients (19,42%) without metastases of 15 patients (18,75 %), with metastases of 5 patients (21.74%) (p = 0.743). Distribution of groups according to morphological variants typical of PR 91 patients (88.35%) without metastases 73 patients (91.25%), with metastases of 18 patients (78.26%), atypical forms of PR 12 patients (11.65%) without metastases 7 patients (8.75%), with metastases of 5 patients (21.74%) (p = 0.087). The degree of histological differentiation of tumors is low 38 patients (36.89%) without metastases 19 patients (23.75%), with metastases 19 patients (82.61%), moderate 52 patients (50.49%) without metastases 48 patients (60 , 0%), metastases of 4 patients (17,39%), high 13 patients (12,62%) without metastases of 13 patients (16,25%), with 0 patients (0) metastases (0) (p <0,001). In the presence of sorghum tumors non-threshold PR 62 patients (60,19) without metastases of 47 patients (58,75%), with metastases of 15 patients (65,22%), pruritus of 41 patients (39,81%) without metastases of 33 patients (41.25%), with the metastasises of 8 patients (34.78%), no significant differences were also found (p = 0.577). Relapse: without relapse, 91 patients (88.35%) without metastases, 80 patients (100%), with metastases of 11 patients (47.83%), relapsing 12 patients (11.65%) without metastases 0 patients (0), with metastases of 12 patients (52.17%) (p <0.001). Statistically significant differences (p <0.001) were determined by the distribution of atypical forms, the degree of histological differentiation of tumors (in the non-metastatic group the moderate degree prevails, whereas in the group with metastases it is low), the presence of relapse, which was manifested only in the metastasis group.

Primary biopsy material of patients with SCCMS for diagnosis was prepared according to standard methods. Sections 4-6 mcm thick were obtained at microtome Microm HM-340m, light microscopy was performed with microscope «Leica DLM-E» (USA), lenses × 10, × 20, × 40, × 100, further IH study was carried out on the basis of the morphological department of the Diagnostic Center of "Pharmacies of the Medical Academy, LLC.", Dnipro.

Table II. The mean expression level of p63 (in%) and correlation with it in the examined patients with squamous cell carcinoma of maxillary sinus, depending on the clinical and morphological variants of the disease

Characteristics	Level of expression of p63, % Me (25 %;75 %)	Differences and relationships between groups
*All examined*i (n=103)	46,0 (35,0; 56,0)	-
Metastases of SCCMS		
SCCMS without metastases	46,0 (36,0; 52,0)	p=0,034* ρ=-0,12 (p=0,212)
SCCMS with metastases	62,0 (26,0; 68,0)	
Relapse of SCCMS		
without relapse (n=91)	42,0 (35,0; 52,0)	p<0,001* ρ=-0,08 (p=0,938)
with relapse (n=12)	65,0 (62,0; 89,0)	
Morphologic variant of tumor		
Typical SC (n=91)	46,0 (36,0; 54,0)	p=0,164* ρ=0,01 (p=0,938)
Atypical forms (n=12)	54,5 (28,0; 89,0)	
Degree of histological differentiation of tumor		
Low (n=38)	46,0 (26,0; 62,0)	p=0,367** ρ=-0,05 (p=0,962)
Moderate (n=52)	42,0 (35,0; 52,0)	
High (n=13)	47,0 (41,0; 47,0)	
Presence of tumor keratinization		
Non-keratinized SC (n=62)	46,0 (38,0; 62,0)	p=0,009* ρ=-0,37 (p<0,001)
Keratinized SC (n=41)	41,0 (26,0; 49,0)	
Expression of caspase-3		
Low (n=34)	42,0 (38,0; 56,0)	p=0,124** ρ=-0,59 (p<0,001)
Moderate (n=52)	46,0 (36,0; 52,5)	
High (n=17)	26,0 (26,0; 68,0)	

Note. * - differences between the groups by Mann-Whitney U test;
** - by nonparametric analysis of variance by Kruskal-Wallis;
associations between groups by Spearman correlation coefficient (ρ)

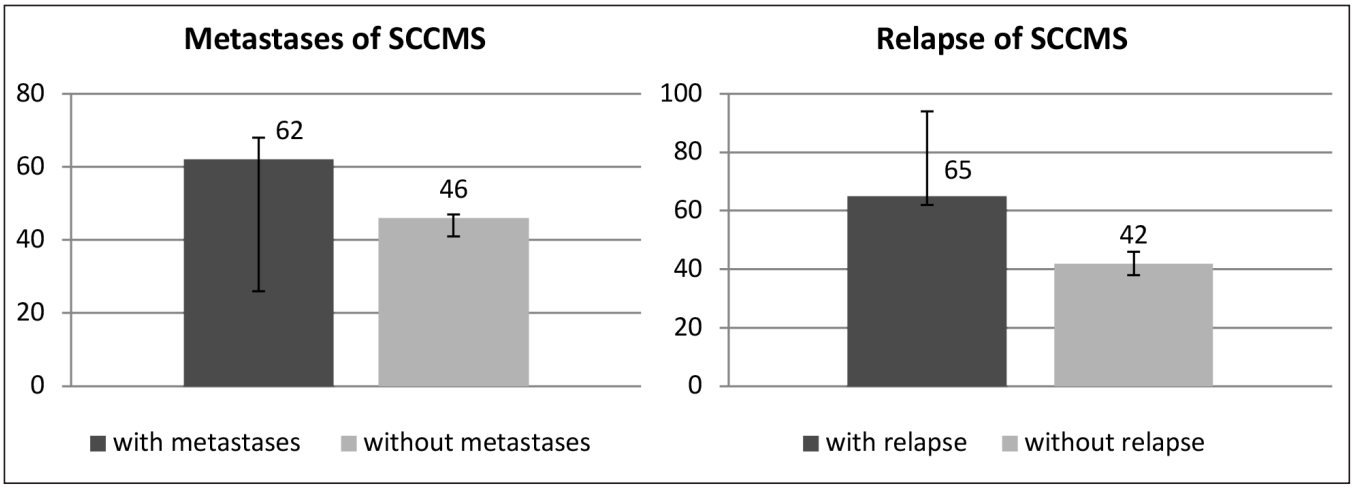


Fig. 2. Median values of expression of p63 (in%) in the groups regarding the presence of metastases and relapses in patients with SCCMS (Me and 95% of CI median)

The level of expression of immunohistochemical markers p63 and caspase-3 by tumor cells and the depth of invasion of tumor cells was determined by photochemical morphometry with "Canon IOS D30" (Japan) digital camera in the DMLS ("Leica" America) microscope and expression indicators were calculated using medical digital image processing program Image J. in the Color Deconvolution cell counter of this program in the integrated scheme of analysis «hematoxylin + DAB.»

Table III. Distribution of expression of p63 indices in the examined patients with squamous cell carcinoma of maxillary sinus

Indices	Level of expression of p63			Differences and relations between groups
	Low	Moderate	High	
All examined (n=103)	22 (21,36)	77 (74,76)	4 (3,88)	-
Metastases of SCCMC, n (% of total number)				
SCCMS without metastases (n=80)	13 (16,25)	67 (83,75)	0 (0)	p<0,001* V=0,46
SCCMS with metastases (n=23)	9 (39,13)	10 (43,48)	4 (17,39)	
Relapse of SCCMS, n (% of total number)				
Without relapse (n=91)	22 (24,18)	69 (75,82)	0 (0)	p<0,001* V=0,57
With relapse (n=12)	0 (0)	8 (66,67)	4 (33,33)	
Morphologic variant of tumor, n (% of total number)				
Typical SCC (n=91)	18 (19,78)	73 (80,22)	0 (0)	p<0,001* V=0,58
Atypical forms (n=12)	4 (33,33)	4 (33,33)	4 (33,33)	
Degree of histologic differentiation of tumor, n (% of total number)				
Low (n=38)	12 (31,58)	22 (57,89)	4 (10,53)	p=0,006* V=0,26
Moderate (n=52)	10 (19,23)	42 (80,77)	0 (0)	
High (n=13)	0 (0)	13 (100,0)	0 (0)	
Presense of keratinization of tumor, n (% of total number)				
Non-keratinized SCC (n=62)	10 (16,13)	48 (77,42)	4 (6,45)	p=0,091* V=0,22
Keratinized SCC (n=41)	12 (29,27)	29 (70,73)	0 (0)	
Expression of caspase-3, n (% of total number)				
Weak (n=34)	0 (0)	32 (94,12)	2 (5,88)	p<0,001* V=0,42
Moderate (n=52)	10 (19,23)	41 (78,85)	1 (1,92)	
High (n=17)	12 (70,59)	4 (23,53)	1 (25,0)	

Note. * - differences between groups according to Pearson's χ2 criterion;
associations between the groups according to V-criterion of Cramer (Cramer's V)

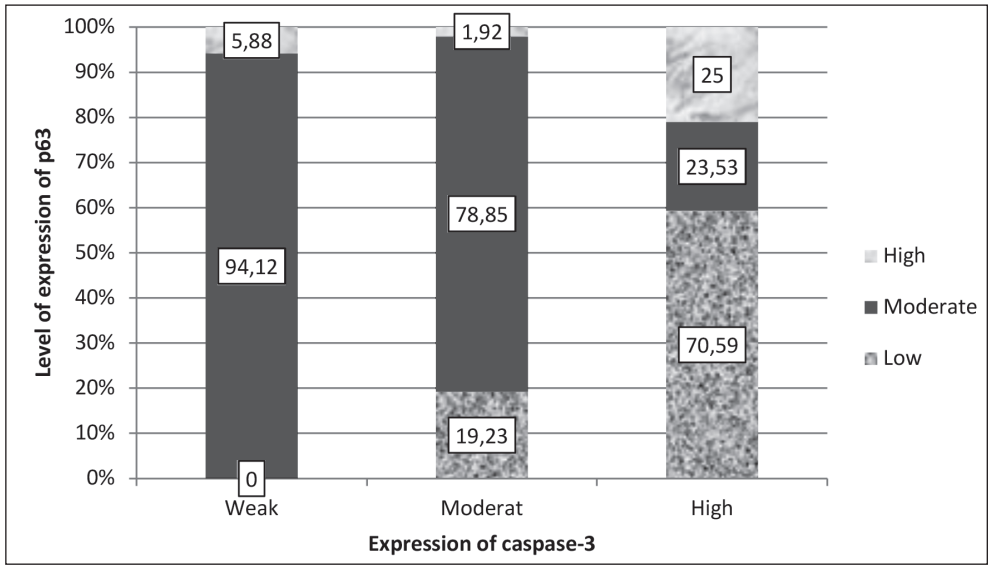


Fig. 3. Distribution of expression of p63 indices in the examined patients with squamous cell carcinoma of maxillary sinus depending on the expression of caspase-3, n (%)

The subject was heard and agreed upon at a meeting of ethics committee of Main Department for Health Care of MI « Mechnikov hospital", protocol №202 from 24.12.12.

Meeting of the Committee on Biomedical Ethics of the Dnipropetrovsk State Medical Academy, protocol №1 from 11.01.13.

Statistical processing was carried out using STATISTICA 6.1 software (StatSoftInc., ser. № AGAR909E415822FA). ROC analysis and construction of ROC curves were carried out in the MedCalc Statistical Software trial version 17.4. (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2017).

Table IV. Estimation of prognostic possibilities of immunohistochemical markers of caspase-3 and ocoprotein p63 in prediction of metastases and relapse of squamous cell carcinoma of MS (according to ROC analysis)

Operation characteristics	Prediction of metastases of SCCMS		Prediction of relapses of SCCMS	
	caspase-3	p63	caspase-3	p63
Sensitivity, %	60,87	60,87	83,33	100,0
Specificity, %	96,25	95,0	35,16	93,41
Area under ROC-curve (AUC)	0,822	0,646	0,609	0,965
Standard error AUC	0,052	0,090	0,077	0,017
95 % confidential interval AUC	0,734 - 0,890	0,546 - 0,738	0,508 -0,704	0,909 - 0,991
Level of significance p	<0,001	0,105	0,154	<0,001
Qualitative estimate of predictive value of marker	very good	moderate	moderate	excellent

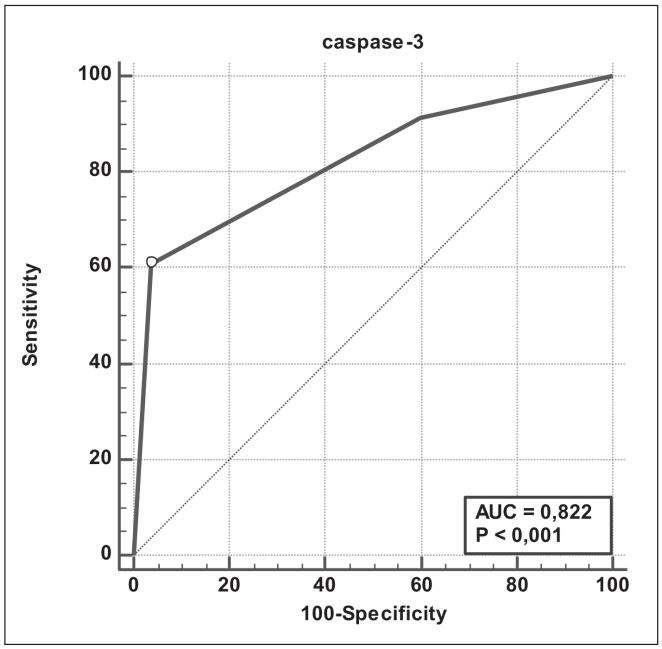


Fig. 4. ROC curve of using caspase-3 expression as a predictor of SCCMS metastases prognosis

RESULTS

The frequency of moderate and high expression rates of caspase-3 in the overall sample was 50.49% and 16.50%, respectively, and a third of cases (33.01%) was characterized by a weak response (Table I). In the group without metastases (p <0.001) moderate expression of the marker (56.25%) prevailed, while in SCCMS group with metastases, it was high (60.87%).

At low and moderate degree of histological differentiation of the tumor, predominantly moderate level of expression of caspase-3 (44.74% and 57.69%, respectively) is observed, whereas at high - mostly weak (61.54%), the differences are statistically significant (p = 0.001), the associative link is average (V = 0.26). Keratinization of the tumor weakly affects (ρ = 0.21; p = 0.038) the level of expression of caspase-3, and predominantly moderate expression of the marker occurs (fig. 1).

The mean expression level of p63 in the examined patients with squamous cell carcinoma of the maxillary sinus was 46.0% (35.0; 56.0) (median and interquartile range). The degree of histological differentiation of the tumor and its morphological variant did not significantly (p> 0.05) exceed the intensity of expression of the oncoprotein (Table II). It should be noted that in the atypical forms of SCC of the maxillary sinus, the expression level of p63 increased on average by 10.0% (95% CI 3.0-30.0), but these changes were statistically unreliable (p> 0.05).

The number of p63-positive specimens was statistically significant (p = 0.034) in the group with metastases compared to non-metastatic cases, the median difference was 13.0% (95% CI 2.0-22.0). The median immunohistochemical marker p63 significantly increased (reliably) (p <0.001) with a recurring course of the disease by 30.0% (95% CI 21.0 - 38.0) compared with the SCCMS without the relapse (fig. 2).

In keratinization of tumors, also statistically significant (p = 0.009) increase of the median expression of p63 by 9.0% (95% CI 2.0 - 15.0) is noted.

In the cells of squamous cell carcinoma of maxillary sinus, the expression of p63 was detected as a specific intracellular staining of varying intensity, mostly moderate (74.76%). In the group of highly differentiated and moderately differentiated SCCMS, the dominant type of staining was of high intensity (100% and 80.77% respectively), whereas in the low-differentiated samples a certain proportion of high (10.53%) and low (31.58%) expression of the marker (Table III) was revealed. The presence of significant differences (p = 0.006) and mean associative links (V = 0.26) of expression of p63 between groups G1, G2, G3 allows to use it as a marker of degree of tumor differentiation.

High P63 expression levels were not detected in SCCMS cells without metastases, whereas in metastases – in 17.39% of samples (p <0.001). The presence of statistically significant differences and relatively strong association links (V = 0.46) between the intensity of expression of p63 and metastases allows to claim about the impact of oncoprotein p63 on metastatic properties of SCCMS.

There were no associations and statistically significant differences (p> 0,05) of expression of p63 indices and keratinization of neoplasm.

A comparative analysis of the levels of p63 and caspase-3 expression (fig. 3) confirmed the reverse correlation be-

Table V. Indices of expression of p63 and caspase-3 in examined patients with SCC of maxillary sinus, depending on the development of papillomas

Indices	SCCMS with development against papilloma (n=81)	SCCMS with development against papilloma (n=22)	Differences and relations between groups
Level of expression of 63, % Me (25 %;75 %)	41,0 (28,0; 47,0)	56,0 (54,0; 68,0)	p<0,001** ρ=0,26 (p=0,008)
Distribution of expression of p63, n (%)			
Low	22 (27,16)	0 (0)	p=0,012* V=0,29
Moderate	57 (70,37)	20 (90,91)	
High	2 (2,47)	2 (9,09)	
Distribution of expression of caspase-3, n (%),			
Weak	22 (27,16)	12 (54,55)	p=0,031* V=0,26
Moderate	46 (56,79)	6 (27,27)	
High	13 (16,05)	4 (18,18)	

Note. * - differences between groups according to Pearson's χ2 criterion;
** - differences between groups according to U Mann-Whitney criterion;
associations between groups according to V-criterion of Cramer's (Cramer's V) and Spearman correlation coefficient (ρ)

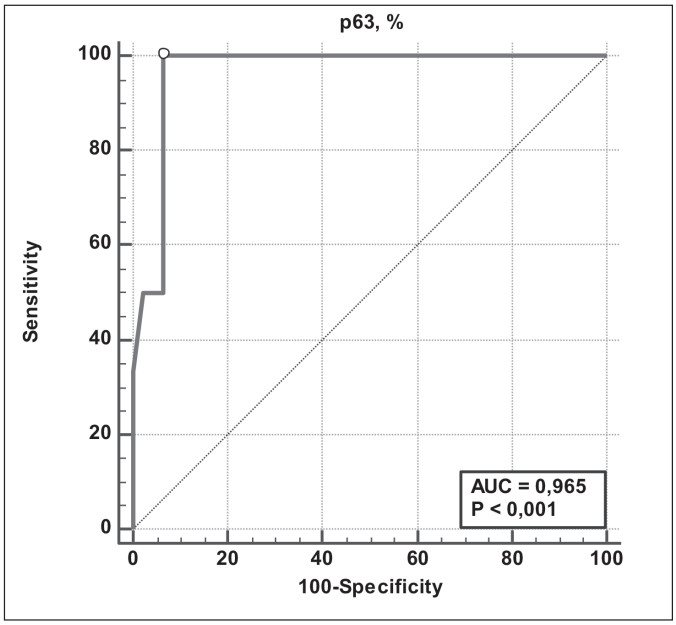


Fig. 5. ROC curve of p63 expression used as a predictor of prognosis of SCCMS relapse

tween them, since the low expression level of p63 is indicated predominantly in the group with high expression of caspase-3 (70.59%), whereas in the group with low expression of caspase-3 only moderate (94.12%) and high (5.88%) levels of p63 (p <0.001) were determined. The presence of relatively strong associations between the biomolecular markers (V = 0.42) was also determined.

Estimation of possibilities of caspase-3 and oncoprotein p63 for predicting metastases and relapses of squamous cell carcinoma of maxillary sinus is given in table IV.

Of the markers analyzed, caspase-3 has higher operating characteristics with regard to metastases prediction: sensitivity - 60.87%; specificity - 96.25%; AUC = 0.822 (p <0.001), which according to the generally accepted classification can be estimated as a very good predictive ability (fig. 4). A higher specificity of caspase-3 compared with sensitivity indicates that the marker expression will accurately identify patients without metastases, since they will not produce false-positive results, which is very important for patients, since no additional testing is required.

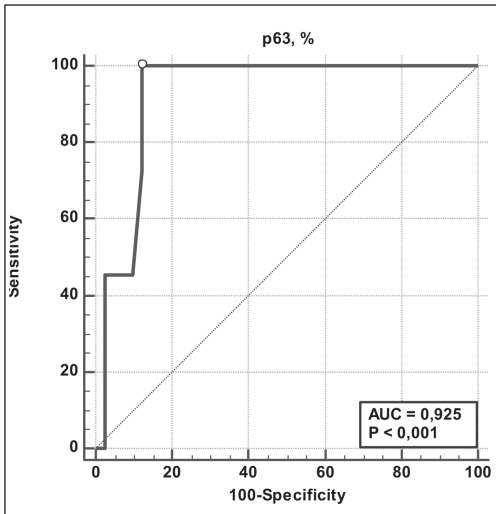
Analysis of expression of p63 and caspase-3 in patients with SCCMS relative to development against papilloma showed certain patterns (table V).

In patients with squamous cell carcinoma of MS developed against papilloma there was detected significantly higher mean level of p63 expression (p <0.001) (the difference of median values - 20.0; 95% CI - 15.0 - 27.0); only moderate (90.91%) and high (9.09%) level of expression of oncoprtein63 by contrast with the comparison group, where weak (27.16%) and moderate (70.37%) cytoplasmic reaction prevailed (p = 0.012); the largest proportion of weak expression of caspase-3 (54.55%) by contrast with the group with SCCMS, developed not against papilloma, where moderate reaction of caspase-3 (56.79%) prevailed (p = 0,031).

Evaluation of relationships between presence of papilloma of maxillary mucosa in the history and rate of expression of caspase-3 and p63 by the Cramer criterion (V = 0.26 and V = 0.269, respectively) showed presence of a moderate association between them. Consequently, squamous cell carcinoma of maxilla with the development against papilloma has a higher probability of a high level of expression of p63 and lower one of caspase-3.

DISCUSSION

The relationship between the presence of metastases and increased expression of caspase-3 is confirmed by the results of the correlation analysis: the Spirman rank co-



Operating characteristics	Indices
Sensitivity, %	100,0
Specificity, %	87,65
AUC	0,925
95 % CI AUC	0,856 - 0,968
p	<0,001
Qualitative assessment of prediction	excellent

Fig. 6. ROC curve and operating characteristics of expression of p63 as a predictor of prognosis of probability of development of SCCMS with papillomas.

efficient ρ = 0,51 (p <0.001); Cramer's criterion V = 0.65, indicating a relatively strong association.

In relapses in caspase-3 a weak associative relation was detected, differences between the groups according to Pearson's χ2 criterion were not detected, however, a certain shift was observed in the level of expression of caspase-3 in relapses towards higher intensity (the proportion of samples with moderate and severe reaction – 83.3%), whereas without relapses - towards the lower intensity (the proportion of sasmples with weak and moderate reaction - 96.25%).

A similar tendency with significant differences (p = 0.031) and mean associative relationship (V = 0.26) was observed in the atypical morphological variant of the tumor - the proportion of samples with moderate and strong expression - 66.67%.

Comparing the level of the oncoprotein p63 in the groups with different expression of caspase-3 by the non-parametric dispersion analysis of Kruskal-Wallis, no differences were found (p = 0.124), which means absence of statistically significant differences in any of the two groups. However, a significant (p <0.001), inverse, moderate correlation (ρ = -0.59) was found between expression of p63 and expression of caspase-3, hence the increase in expression of one marker studied is associated with a decrease in the expression of another. Also, a reliable feedback of the level of expression of p63 with keratinization of the tumor was found (ρ = -0.37; p <0.001).

Among tumors with relapses, the number of p63-positive with the intense reaction made up 33.33%, which is significantly (p <0.001) higher than in non-relapsed tumors, which is confirmed by a relatively strong association (V = 0.57) of expression of p63 with the early development of relapses in SCCMS.

Also significant discrepancies and significant associations between the degree of expression of p63 and morphological variants of tumors were found.

It has been determined that the likelihood of metastases of SCC of maxillary sinus at a high expression level of p63 is higher than in tumors with low and moderate levels of oncoprotein (OR = 37.15; 95% CI (1.92 - 719.42); p = 0.017) as well as a probability of recurrence (OR = 96.88; 95% CI (4.80 - 1955.95); p = 0.003).

By estimate of odds ratio, the likelihood of development of metastases of SCCMS in a high expression of caspase-3 is greater than with a weak and moderate reaction (odds ratio = 39.93; 95% CI (1.92 - 719.42); p = 0.017). Statistically significant odds ratio prevalence as for relapse of SCCMS in a high expression of caspase-3 was not detected.

Regarding the prognostic capabilities of p63 relative to metastases, in similar to caspase-3 operating characteristics (sensitivity of 60.87%, specificity of 90.5%), the area under the ROC curve (AUC = 0.664) for the prognostic ability of the oncoprotein has not reached a sufficient level and does not have statistically significant level (p> 0.05).

For prediction of recurrence of squamous cell carcinoma of maxillary sinus, statistically significant operating characteristics were detected only in p63: sensitivity - 100.0%, specificity - 93.41%; AUC = 0.965 (p <0.001), which according to the generally accepted classification of the area under the curve, can be considered as excellent predictive characteristics (fig. 5). Informativity of caspase-3 for such a prediction is moderate: the area under the ROC curve makes up only AUC = 0.609, being statistically insignificant (p = 0.154).

A pair comparison of ROCs between curves was not meaningful, since markers analyzed had statistically significant operating characteristics only for one type of prediction: caspase 3 – for predicting metastasis, p63 - for relapse.

It should be noted that marker p63 also has excellent operating characteristics with regard to diagnostic ability for predicting probability of developing squamous cell carcinoma of maxillary sinus in patients with papillomas of the maxillary mucosa (fig. 6).

ROC analysis showed excellent discriminatory ability for p63 to predict the likelihood of development of SCCMS with papillomas: sensitivity - 100.0%, specificity - 87.65%; AUC = 0.925 (p <0.001).

CONCLUSIONS

Based on the results of the study performed, it can be argued that expression of caspase-3 and p63 has a significant effect on the clinical and morphological properties of squamous cell carcinoma of maxillary sinus, its course and aggressiveness.

The presence of significant differences in expression of caspase-3 between tumor groups of varying degrees of histological differentiation (predominantly moderate level of expression of caspase-3 in a low differentiation of the tumor - 44.74% and weak in high - 61.54%; p = 0.001) and the morphological variant of the tumor allows to use it as an appropriate biomolecular marker.

There was detected a relatively strong association relationship of increase in expression of caspase-3 with SCCMS metastases (V = 0.65; ρ = 0.51 (p <0.001); OR = 39.93; 95% CI (1.92-719; 42)) and absence of correlation of immunohistochemical reaction of this marker with the development of relapses.

Expression of caspase-3 increases in the cells of the malignant tumors of SCCMS, which leads to suppression of apoptosis, changes in the characteristics of tumor cells and their stimulation to metastases.

This is confirmed by the results of the performed ROC analysis, according to which caspase-3 does not have sufficient information value to predict the recurrence of squamous cell carcinoma of maxillary sinus and has a very probable prognostic capacity as a marker for prediction of metastasis of SCCMS (area under the curve AUC0.822 (p <0.001); sensitivity - 60.87%, specificity - 96.25%). So, the study of caspase-3 expression can be used in clinical practice to predict metastases of SCCMS.

The increase in the level of expression of caspase-3 leads to the decrease in the expression of p63, an inverse correlation relationship is established between immunohistochemical reactions of markers (ρ = -0.59 (p <0,001), V = 0.42). The low level of expression of p63 is noted mainly in the group with high expression of caspase-3 (70.59%; p <0.001), which indicates its anti-differentiation and anti-apoptotic role, participation in the suppressive mechanism of apoptosis of the tumor.

Oncoprotein p63 can be used as a biomarker for the development and progression of the tumor. According to the ROC analysis, based on the expression level of p63, the probability of development of SCCMS with papillomas (AUC = 0.925 (p <0.001), sensitivity of 100.0%, specificity of 87.65%) and the development of recurrence of squamous cell carcinoma of the maxillary sinus (AUC = 0.965 (p <0.001), sensitivity 100.0%, specificity 93.41%), since the marker has excellent prognostic characteristics for them.

In the increased expression level of p63, the chances for development of SCCMS recurrence increase (compared with the low and moderate levels of the oncoprotein - OR 96.88, 95% CI (4.80 - 1955.95), a relatively strong associative relationship V = 0, 57) and metastasis (HS = 37.15, 95% CI (1.92 - 719.42); relatively strong associative relationship V = 0.46). The difference in the median values of p63-positive samples in the SCCMS group with metastases compared with those without metastases was 13.0% (95% CI 2.0-22.0);in a recurrent course of the disease in comparison with SCCMS, without recurrence - 30.0% (95% CI 21.0 - 38.0).

Thus, markers analyzed have statistically validated characteristics regarding the prognosis of probability of development of SCCMS against the background of papilloma (p63); degree of histological differentiation of the tumor (p63 and caspase-3), for prediction of metastases (caspase 3) and relapse (p63) of cancer. Due to the use of prognostic biomolecular markers caspase-3 and p63, a contingent of patients with an increased risk of adverse aggressive course of squamous cell carcinoma of the SCCMS can be selected, which will significantly reduce the cost of further diagnostic examinations and will make it possible to develop optimal therapeutic tactics.

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ORIGINAL ARTICLE
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THE IMPACT OF GROUP AND INDIVIDUAL TRAINING ON HEMODYNAMICS, LIPID METABOLISM, PHYSICAL ACTIVITY AND QUALITY OF LIFE IN PATIENTS WITH HIGH AND VERY HIGH CARDIOVASCULAR RISK

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ABSTRACT

Introduction: Despite significant advances in prevention and treatment, cardiovascular disease remains the main cause of mortality and disability in Europe. This is largely due to the low level of commitment to doctors' recommendations for drug treatment and lifestyle modification.

The aim of the study was to compare the effectiveness of group and individual training in the basics of medical knowledge to control the main risk factors for cardiovascular disease in patients.

Materials and methods: The study included 210 patients with high and very high cardiovascular risk. The first group consisted of 75 patients who studied at the School of Health 'Fundamentals of Healthy Lifestyle'. The second group consisted of 75 patients who were offered individual counseling. The control group consisted of 60 individuals. Patients in both groups were examined before and after the end of the course.

Results and conclusions: We conducted a general clinical examination, determined anthropometric parameters, blood pressure (BP), glucose, cholesterol and its fractions in the blood. It has been established that the group training of patients with high and very high cardiovascular risk in Schools of Health 'Fundamentals of Healthy Lifestyle' promotes better BP control, but does not significantly affect the lipid metabolism. Individual training for patients with high and very high cardiovascular risk leads to a significant reduction in BP levels, improved lipid metabolism, increased physical activity, and improved quality of life.

KEY WORDS: cardiovascular risk, patient education, hemodynamics, lipid spectrum of blood, physical activity, quality of life

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INTRODUCTION

Despite significant advances in prevention and treatment, cardiovascular disease remains the main cause of mortality and disability in Europe [1]. This is largely due to the low level of commitment to doctors' recommendations for drug treatment and lifestyle modification. Compliance with drug treatment remains extremely low in most countries of the world [2-5]. It is even more difficult to influence the patient's lifestyle. According to the National Health and Nutrition Examination Survey 2011-2012, only 1.8% of people over the age of 50 years and older are healthy nutritionists and only 37.1% have 150 minutes of moderate physical activity or 75 minutes of severe physical activity per week [6]. The poorest socioeconomic status and/or low educational level show the worst commitment to a healthy way [7].

Various strategies are available to improve people's commitment to a healthy lifestyle. Undoubtedly, government programs have been shown to be effective in limiting lipids in food products, controlling the sale of alcohol or tobacco products, excessively high cigarette prices, material incentives for bicycle use or regular physical training, and active information policy with the involvement of social advertising and television [8]. All of the above strategies require state involvement and appropriate funding.

One of the effective ways to increase compliance with the doctor's recommendations is to train patients in the basics of medical knowledge. The efficacy of this approach in the management of stroke patients [9] or myocardial infarction [10] has been shown to affect diabetes mellitus (DM) [11, 12] and obesity [13]. The training can be conducted both in groups, and individually.

THE AIM

The aim of the study was to compare the effectiveness of group and individual training patient in basic medical knowledge to control the main risk factors for cardiovascular disease.

MATERIALS AND METHODS

The research was carried out on the basis of the Department of Complex Risk Reduction of Chronic non-Communicable Diseases of the Government Institution 'L.T. Malaya

Therapy National Institute of the National Academy of Medical Sciences of Ukraine' (Kharkiv, Ukraine) during 2016-2018. The training of patients was carried out either at the Schools of Health, or individually in a doctor-patient mode. The study involved 5 doctors (2 cardiologists, 1 endocrinologist, 1 dietician and 1 dentist), 1 instructor of physical education and 1 nurse. The doctors conducted classes with patients were not their treating physician. Patients had the opportunity at any time to turn to their treating physician for correction of therapy.

STUDY GROUPS

The study included patients with high and very high cardiovascular risk. The inclusion criteria for the study were: signed informed consent; high and very high cardiovascular risk; the desire and opportunity to continue the drug therapy that was chosen in the hospital; absence of side effects associated with medication therapy; absence of significant violations of the cognitive function; high level of adherence to medical treatment. Criteria for exclusion from the study were: oncological diseases; insulin-dependent DM; thyroid dysfunction; heart failure (HF) IV functional class (FC); depressive disorders; disturbance of the locomotor apparatus, which significantly limits the physical activity; planned surgical intervention; the impossibility for any reason to continue the medical therapy prescribed in hospital; acute inflammatory processes.

Patients were divided into groups by randomization with sealed envelopes: 75 patients undergone group training in Schools of Health (group 1), 75 patients undergone individual training (group 2) and 60 patients entered the control group (group 3). Total duration of study in groups was 1 year. At the beginning and at the end of the study, we determined blood pressure (BP), glucose and lipid levels in blood, anthropometric indices, physical activity and muscle contraction strength and indicators of quality of life.

Groups did not differ in age and gender ratios. Groups 1, 2 and 3 were not significantly different in terms of the number of patients with DM; arterial hypertension (AH); patients with a history of myocardial infarction or revascularization. The distribution of AH grades and functional classes of heart failure (NYHA) in groups was also comparable (Table 1).

PATIENT EDUCATION METHODS

Group training consisted of 9 classes with frequency 1 time per month (duration was 1 hour). Each session consisted of 4 lectures (15 minutes each) and was devoted to one of the most common chronic non-infectious diseases: coronary artery disease (CAD), AH, DM, diseases of the musculoskeletal system, thyroid gland, age-associated lesions of the central nervous system. Particular attention was paid to the main risk factors of the disease and methods for their correction. Classes were conducted by a cardiologist, dietician and instructor of physical education. At the beginning of the cycle, patients were given methodical materials and an individual diary. After each lesson, patients received tasks that they performed in an individual diary.

Patients from an individual group also visited the clinic once a month. There were 9 visits in total. The cardiologist, endocrinologist, dietician, dentist and instructor of medical physical education communicated with the patient in turn (one by one). The duration of the individual consultation with each specialist was 15 minutes. Patients also received tasks that were performed in an individual diary.

INSTRUMENTAL EXAMINATION

All patients BP, body weight, height were measured; the ratio of fat and muscle tissue was estimated as well as physical activity was determined (with the help of pedometers).

Measurement of BP levels was carried out in accordance with the current recommendations of the European Society of Cardiology [14].

Determination of anthropometric indicators took place in light clothing, without shoes, in the first half of the day. All measurements were carried out by a trained nurse. The height (cm) and body weight (kg) were determined; the body mass index (BMI) was calculated by the formula:

$$BMI = \text{body weight (kg)} / \text{height}^2 (m^2)$$

The body composition (the amount of fat and muscle tissue, visceral fat) was determined by the method of bioelectric impedance on the device Body Composition Monitor BF511 (Omron, China).

The physical activity was assessed by the number of steps per day using the Walking Style III pedometer (Omron, China).

LABORATORY EXAMINATION

Blood sampling to determine glucose cholesterol levels was performed on an empty stomach, after a 9 hour interval food intake, in the first half of the day from a cubital vein, in a volume of 10 ml. Levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL) were determined by the enzymatic method on the biochemical analyzer HumaStar 200 (Human, Germany). Very low density lipoprotein (VLDL) cholesterol was calculated according to the formula: VLDL cholesterol = TG / 2.2. Low density lipoprotein (LDL) cholesterol was calculated by Friedewald W.T. formula [15]: LDL cholesterol (mmol/l) = total cholesterol - HDL - TG / 2.2. The level of glycemia was determined by the glucose oxidase method on the biochemical analyzer HumaStar 200 (Human, Germany).

ASSESSMENT OF THE ACHIEVEMENT OF THE TARGETS

Achievement of target BP and lipid metabolism rates were evaluated in accordance with the current recommendations of the European Society of Cardiology [14, 16]. The target LDL cholesterol level for patients with very high cardiovascular risk was 1.8 mmol/l. According to current guidelines, for patients with high cardiovascular risk, the target LDL

Table 1. Clinical characteristics of patients

Nosological forms			Group training, n =75 Group 1	Individual training, n =75 Group 2	Control group, n=60 Group 3	c^2, p
			1	2	3	
AH		Without AH	6 (8.0 %)	10 (13.3 %)	3 (5.0 %)	0.63. p_{1-2}=0.428 0.12. p_{1-3}=0.727 1.79. p_{2-3}=0.181
		Grade 1	0	3 (4.0 %)	3 (5.0 %)	1.36. p_{1-2}=0.244 1.88. p_{1-3}=0.170 0.02. p_{2-3}=0.889
		Grade 2	45 (60.0%)	46 (61.3 %)	38 (63.3 %)	0.03. p_{1-2}=0.867 0.05. p_{1-3}=0.828 0.01. p_{2-3}=0.953
		Grade 3	24 (32.0 %)	16 (21.3 %)	16 (26.7 %)	2.18. p_{1-2}=0.139 0.45. p_{1-3}=0.500 0.27. p_{2-3}=0.603
Coronary artery disease	Stable angina	Without stable angina	11(14.7 %)	18 (24.0 %)	10 (16.7 %)	2.09 p_{1-2}=0.148 0.10. p_{1-3}=0.750 1.09. p_{2-3}=0.297
		I FC	4 (5.3 %)	7 (9.3 %)	5 (8.3 %)	0.39 p_{1-2}=0.531 0.12. p_{1-3}=0.729 0.01. p_{2-3}=0.919
		II FC	52 (69.3 %)	47 (62.7 %)	41(68.3 %)	0.74 p_{1-2}=0.389 0.48. p_{1-3}=0.491 0.01. p_{2-3}=0.951
		III FC	8 (10.7 %)	3 (4.0 %)	6 (10.0 %)	1.57 p_{1-2}=0.210 0.02. p_{1-3}=0.845 1.08. p_{2-3}=0.298
	The history of myocardial infarction		22 (29.3 %)	18 (24.0%)	16 (26.7 %)	0.55. p_{1-2}=0,460 0.12. p_{1-3}=0,732 0.13. p_{2-3}=0,723
	Revascularization		11 (14.7%)	10 (13.3 %)	9 (15.0 %)	0.06. p_{1-2}=0,814 0.00. p_{1-3}=0,957 0.08. p_{2-3}=0,782
HF (NYHA)		Without HF	16 (21.3 %)	16 (21.3 %)	9 (15.0 %)	0.89. p_{1-3}=0.347 0.89. p_{2-3}=0.347
		I FC	6 (8.0 %)	6 (8.0 %)	5 (8.3 %)	0.09. p_{1-2}=0.814 0.06. p_{1-3}=0.806 0.06. p_{2-3}=0.806
		II FC	45 (60.0 %)	50 (66.7 %)	39 (65.0 %)	0.72. p_{1-2}=0.397 0.17. p_{1-3}=0.677 0.04. p_{2-3}=0.839
		III FC	8 (10.7 %)	3 (4.0 %)	7 (11.7 %)	1.57. p_{1-2}=0.210 0.01. p_{1-3}=0.927 1.85. p_{2-3}=0.174
Type 2 DM			21 (28.0 %)	23 (30.7 %)	15 (25.0 %)	0.13. p_{1-2}=0.720 0.15. p_{1-3}=0.695 0.53. p_{2-3}=0.467

cholesterol level was 2.5 mmol/l. The percentage of patients with target LDL levels in each group was calculated up to the beginning of training and after 1 year of participation in the program.

THERAPY

The study involved patients who had been treated at the Government Institution 'L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of

Table 2. Drug therapy at the time of inclusion in the study

Groups of drugs	Group training, n =75 Group 1	Individual training, n =75 Group 2	Control group, n=60 Group 3	p
	1	2	3	
Antiplatelet	74 (98.7 %)	73 (97.3 %)	58 (96.7 %)	p_{1-2}=0.541 p_{1-3}=0.347 p_{2-3}=0.917
Angiotensin-converting enzyme inhibitors	58 (77.3 %)	57 (76.0 %)	51 (85.0 %)	p_{1-2}=0.851 p_{1-3}=0.245 p_{2-3}=0.1
Antagonists of angiotensin II receptors	12 (16.0 %)	10 (13.3 %)	7 (11.7 %)	p_{1-2}=0.641 p_{1-3}=0.477 p_{2-3}=0.822
Blockers of beta-adrenergic receptors	47 (62.7 %)	45 (60.0 %)	42 (70.0 %)	p_{1-2}=0.735 p_{1-3}=0.395 p_{2-3}=0.230
Diuretics	51 (68.0 %)	50 (66.7 %)	38 (63.3 %)	p_{1-2}=0.865 p_{1-3}=0.569 p_{2-3}=0.6
Antagonists of calcium channels	12 (16.0%)	16 (21,3%	9 (15.0%)	p_{1-2}=0.402 p_{1-3}=0.873 p_{2-3}=0.347
Ivabradin	3 (4.0 %)	2 (2.7 %)	1 (1.7 %)	p_{1-2}=0.659 p_{1-3}=0.436 p_{2-3}=0.792
Metformin	17 (22.7 %)	18 (24.0 %)	12 (20.0 %)	p_{1-2}=0.851 p_{1-3}=0.675 p_{2-3}=0.580
Statins	75 (100.0 %)	75 (100.0 %)	60 (100.0 %)	

Ukraine' (no earlier than 3 months after discharge from the hospital). Only those patients who took all prescribed medications before discharge from the hospital, had no side effects associated with medication therapy, agreed with the therapy and had the opportunity to continue it, were invited to participate in this scientific program. The therapy was prescribed by doctors of the Government Institution 'L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine' in accordance with existing recommendations for the treatment of AH, CAD, DM, dyslipidemia [14, 16, 17]. Table 2 shows the groups of drugs that patients received when included in the study.

QUESTIONNAIRE

Indicators of quality of life were determined according to the questionnaire (using the Health Status Survey SF-36 questionnaire). Each patient was provided with free premises, pre-conducted instruction, the patient self-filled questionnaire.

Compliance to drug treatment was determined using the Mauriceki-Green scale at the inclusion stage and after completing the full cycle of training. The study included only patients who had a high degree of compliance to drug therapy at the stage of involvement in the study [18].

ETHICAL ASPECTS OF THE STUDY

The protocol of the study was approved by the local ethics commission of the Government Institution 'L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine'. The study was carried out in accordance with the principles of the Helsinki Declaration. All patients signed an agreement to participate in the study.

STATISTICAL PROCESSING OF DATA

The statistical processing of the obtained data was carried out using the package of statistical software "SPSS 17" (IBM), Microsoft Office Exel-2003. Normality of data distribution was estimated by Kholmogorov-Smirnov method. The data corresponding to the normal distribution were presented in the form of averages and mean errors. Data that did not meet the criteria for normal distribution were represented as median and 25% and 75% quartiles. Reliability was assessed using Student t-test when comparing the mean values and the c^2 method when comparing the frequencies with which the signs in the groups occurred.

RESULTS

Before the study, the BP in the groups did not differ significantly: the difference in the groups 1, 2 and 3 by the

Table 3. Dynamics of hemodynamic parameters in patients with high and very high cardiovascular risk

Indicator	Before	After	P
Group training			
SBP, mmHg	134.9±15.5	124.6±9.5	0.010
DBP, mmHg	85.8±9.7	78.1±7.7	0.012
Individual training			
SBP, mmHg	133.3±15.6	123.3±11.8	0.006
DBP, mmHg	83.±8.9	78.6±7.8	0.005
Control group			
SBP, mmHg	134.7±11.2	131.9±10.5	0.160
DBP, mmHg	84.5±10.6	82.2±9.7	0.218

Table 4. Dynamics of lipid and carbohydrate metabolism parameters in patients with high and very high cardiovascular risk

Indicator	Before	After	P
Group training			
Total cholesterol, mmol/l	5.26±1.62	5.62±1.27	0.088
HDL cholesterol, mmol/l	1,42±1.36	1.36±1.15	0.316
Triglycerides, mmol/l	1.78±0.98	1.81±0.67	0.769
LDL cholesterol, mmol/l	3.21±0.52	3.43±0.67	0.410
Glucose, mmol/l	5.78±1.1	5.98±1.5	0.385
Individual training			
Total cholesterol, mmol/l	5.34±1.1	4.41±1.4	0.002
HDL cholesterol, mmol/l	1.14±0.25	1.49±0.24	0.03
Triglycerides, mmol/l	1.71±0.37	1.60±0.70	0.231
LDL cholesterol, mmol/l	3.22±0.96	2.68±0.81	0.005
Glucose, mmol/l	5.34±1.1	4.53±0.9	0.001
Control group			
Total cholesterol, mmol/l	5.31±1.2	5.12±0.9	0.329
HDL cholesterol, mmol/l	1.19±0.37	1.21±0.22	0.720
Triglycerides, mmol/l	1.68±0.72	1.71±0.68	0.815
LDL cholesterol, mmol/l	3.12±0.94	2.98±1.2	0.478
Glucose, mmol/l	5.09±1.15	4.70±1.04	0.053

level of systolic BP (SBP) was: p1-2 = 0.530, p1-3 = 0.933 and p2-3 = 0.560, and by the level of diastolic BP (DBP) it was: p1-2 = 0.150, p1-3 = 0.460 and p2-3 = 0.593 (Table 3).

In both groups of studies, there was a significant decrease in BP levels. In the control group, the rates did not change statistically significantly. Also in both groups of study, an increase in the number of patients with target BP was established. If at the beginning of the study, the number of patients with target BP levels was 31 (41.8%) among patients in group 1 and 46 (60.9%) among patients in group 2, then at the end of the study, these rates significantly increased in both groups of patients - 59 persons (78.4%, p=0.0001) and 69 persons (92%, p=0.0001), respectively. The levels of SBP and DBP decreased by 8.3% (p=0.001) and 10.0% (p=0.004) in patients of group 1 and 8.2% (p = 0.002) and 6.2% (p = 0.001) in patients of group 2 (Table 3).

At the beginning of the study, LDL cholesterol did not differ in 1, 2 and control groups: p1-2 = 0.937, p1-3 = 0.435 and p2-3 = 0.586 (Table 4). At the beginning of the study, the number of patients with target LDL cholesterol levels in group 1 was 8 persons (10.6%), in group 2 - 2 persons (2.7%), at the end of the study - 16 people (21.6%, p=0.084) and 6 persons (8.0%, p=0.078), respectively. In group 1, lipid metabolism rates did not significantly change. At the same time, in group 2, a statistically significant decrease in the level of total cholesterol by 21.1% (p=0.031), LDL cholesterol by 20.1% (p=0.04) and an increase in HDL cholesterol by 11% (p=0.03).

Before and after the study, blood glucose level was normal in all three groups. At the same time in group 2, it has significantly decreased (Table 4).

Assessment of adherence to treatment was carried out at the stage of inclusion in the study and after the completion

Table 5. Dynamics of anthropometric indices of patients with high and very high cardiovascular risk

Indicator	Before	After	P
Group training			
BMI, kg/m^2	33.0±7.1	33.6±6.3	0.637
Fatty tissue, %	40.9±9.2	42.0±8.2	0.476
Visceral fat, %	12.6±4.6	12.6±4.7	0.989
Muscle tissue, %	25.4±4.86	25.4±3.3	0.965
Individual training			
BMI, kg/m^2	31.8±5.7	29.8±4.1	0.011
Fatty tissue, %	38.9±6.1	35.3±6.1	0.013
Visceral fat, %	12.4±4.8	10.7±3.8	0.020
Muscle tissue, %	25.1±4.6	24.9±6.9	0.805
Control group			
BMI, kg/m^2	32.1±4.9	30.8±5.1	0.157
Fatty tissue, %	39.1±7.2	38.3±6.8	0.533
Visceral fat, %	12.6±4.1	11.9±5.4	0.426
Muscle tissue, %	24.6±6.5	24.9±5.8	0.790

of the full cycle of training (in the control group in one year). The study involved only patients who had 4 points on the Morriscoe-Green scale. Upon completion of the study, the level of compliance to the medical treatment in the group that was trained in the schools of health was 3.5 [1.5-3.5], in the group of individual training 3.5 [2.0-3.5] and in the control group 2.0 [1.0-3.0]. According to this indicator group 1 and 2, after the completion of the training, did not differ statistically significantly.

Before the start of training, groups 1 and 2 were not statistically significantly different of anthropometric indicators among themselves and indicators of the control group. Anthropometric indices of group 1 patients, as well as indicators that characterize body composition have not significantly changed (Table 4). At the same time, in the group of individual training, a significant decrease in BMI (7%, p=0.011), fatty tissue (10.2%, p=0.013), visceral fat (13.4%, p=0.020) was established. In the control group, there were no statistically significant changes in anthropometric indices (Table 5).

It should be noted that the number of patients with BMI <30 kg/m^2 at the beginning and at the end of the study, in patients with group training (28 (37.5%) and 24 (32.4%), p=0.493) as well as in patients with individual training (47 (62.5%) and 50 (66.7%), p=0.608) did not significantly change. At the same time, the physical activity assessed by the number of steps per day, did not change in the first group (2311.61±672.44 and 2033.33±980.27, p=0.205), but significantly increased in the second group (from 2346.67±845.54 to 2654.67±722.08, p=0.007).

In the first group, the quality of life estimated by the questionnaire (using the Health Status Survey SF-36 questionnaire) was not significantly change (58.66±16.21 and 62.54±16.39, p=0.062), however, in the second the group it was significantly increased (from 58.16±9.88 to 67.21±14.34, p=0.008). Statistically significant changes in quality of life in the control group have not been established (57.31±16.21 and 58.51±16.39, p=0.688).

To compare the effectiveness of group and individual training with a long observation period (follow up was 3 years), Kaplan-Meier analysis was performed. We used combined endpoints for evaluation: cardiovascular death, strokes, infarcts, unstable angina, progression of heart failure, and acute revascularization (Figure 1). It was established that in the group of individual training, there were a statistically significantly lower number of cardiovascular events.

DISCUSSION

The results of our study indicate a higher effectiveness of individual training compared with group training. Thus, the educational program 'Fundamentals of Healthy Lifestyle' only contributes to improving BP control and does not affect the cholesterol level and anthropometric indicators. At the same time, patients of individual training group marked a significant decrease in BP levels, increased physical activity, improved lipid metabolism and quality of life.

As for our results, it should be noted that we were tasked with assessing how much training (raising the level of medical knowledge) contributes to controlling risk factors: high BP, dyslipidemia, overweight and low physical activity. Our study did not have the purpose of interfering with the work of the doctor (changing the treatment regimens, a higher frequency of visits, etc.). The study was based on the concept of self-care as a factor affecting the course of chronic non-communicable diseases [19]. Our data are consistent with the results of other studies, which show that educational programs contribute to more effective control of BP [20] and dyslipidemia [21]; training patients is one of the key not only in the treatment of diabetes but also

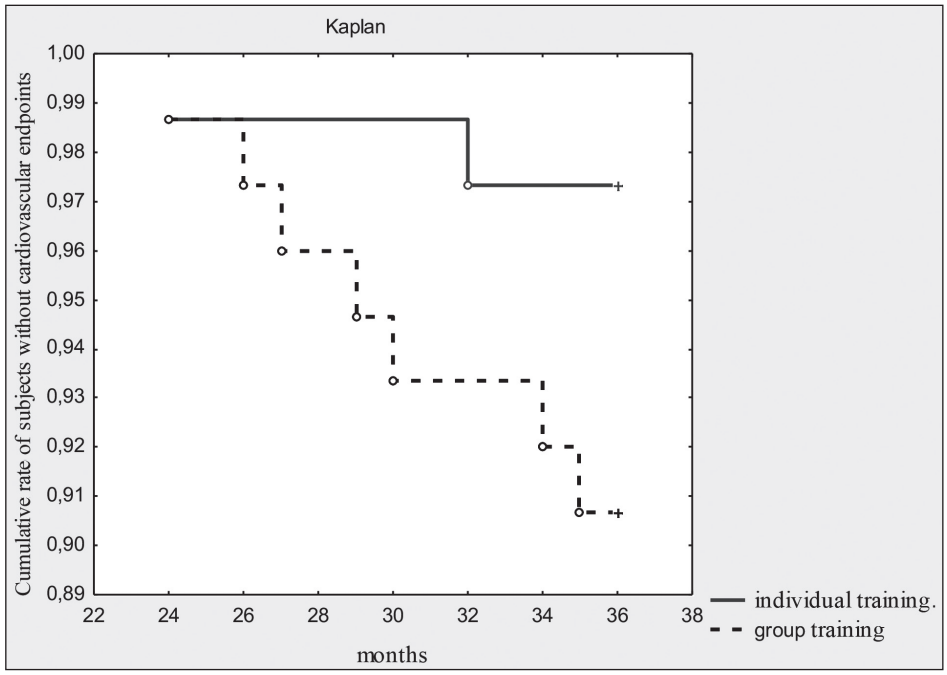

Figure 1. Kaplan-Meier estimator.

in its prevention [22]. Smith R. et al. found that women's awareness of CAD affects decision making on treatment and prevention by patients [23]. Lee E. and Park E. have shown that training patients along with family support contributes to higher BP control [24]. The effectiveness of active involvement of the patient in the treatment process has been demonstrated by Captieux M. et al. in the management of patients with type 2 DM [25].

However, our data do not fully agree with the results of other researchers. Thus, in a number of studies the clinical efficacy of group educational programs has been proved. According to researchers, studies at the Schools of Health on Arterial Hypertension contributed not only to improving control of BP [26] and cholesterol in the blood [27], but also led to an increase in physical activity [28].

In 2017, the results of the Cochrane systematic review were published, which summarized 22 studies (76 864 patients with coronary artery disease). The influence of the educational component of cardiac rehabilitation on the mortality rates, the frequency of fatal and nonfatal myocardial infarction, revascularization, hospitalization, and quality of life in patients with coronary heart disease were studied. Programs differed in intensity from one 40-minute face-to-face session plus a 15-minute follow-up call to daily lessons for 4 weeks in a hospital with subsequent sessions for 11 months. It was shown that training did not affect the indicators of overall mortality, the frequency of fatal and nonfatal myocardial infarction, revascularization, or hospitalization. Improvement of separate indicators of quality of life related to health was noted in the group of patients who underwent training as compared to non-trained patients [29].

One of the most important data in our study was LDL cholesterol levels before and after training. It is known that data on the achievement of LDL cholesterol target levels significantly differ in clinical randomized trials and in real clinical practice. All patients included in our study, were prescribed statins (atorvastatin or rosuvastatin). The average dose of atorvastatin in group training was 29.18±9.22 mg per day, in the group of individual training - 32.4±10.34 mg per day (p=0.192). The daily doses of rosuvastatin in group and individual training were 27.72±8.46 and 26.1±7.81 mg (p=0.282), respectively. In the control group, patients received 30.1±7.9 mg of atorvastatin or 27.2±11.4 mg of rosuvastatin (p=0.441). Of course, one of the limitations of this study is the insufficiently high doses of statins; at the same time, our data reflect actual clinical practice in Ukraine. World over, the results obtained for lipid metabolism correction using statins are extremely different in clinical randomized trials and in real clinical practice [30]. Thus, the study DYSIS (Dyslipidemia International Study) has shown insufficient control of lipid metabolism in most countries. In the countries of the Baltic (1797 people with cardiovascular disease) among subjects who regularly received statins, target LDL cholesterol levels were observed only in 19.4% of patients [31]. In Austria, among 910 patients treated with statins, 59.1% had elevated total cholesterol, 52.3% had excessive LDL cholesterol, and 23% had low levels of HDL cholesterol [32]. In Lebanon and Jordan (617 people who took statins for 3 months), 55.9% did not reach the target levels of LDL cholesterol [33]. In Canada (2436 patients with high cardiovascular risk), in regular statins intake, the target level of LDL cholesterol did not reach 37% of subjects [34]. In the United States, according to a retrospective analysis of high-risk cardiac patients taking statins, target LDL cholesterol levels reached 20-26% and LDL cholesterol - 67-77% of patients [35]. The EUROASPIRE IV study showed that among patients with CAD, statins were received in 85.7% of patients, with less than 20% reaching the target levels of LDL cholesterol [36]. Of course, one of the causes of this phenomenon may be insufficient compliance, the second - insufficient high doses of statins, but in our study

we included only patients who demonstrated a high degree of commitment to therapy. Our data on cholesterol lowering may be due to insufficiently high doses of statins, but in general, our data do not contradict these studies conducted in real clinical practice.

LIMITATION OF THE STUDY

The study was conducted with the participation of a small number of patients and limited to one year of observation. Women dominated in all groups. A small number of participants was due to the selection of patients with high compliance and the opportunity to attend classes regularly.

CONCLUSIONS

1. Group training of patients with high and very high cardiovascular risk in Schools of Health 'Fundamentals of Healthy Lifestyle' promotes better BP control, but does not significantly affect the lipid metabolism.
2. Individual training of patients with high and very high cardiovascular risk leads to a significant decrease in BP levels, improved lipid metabolism, increased physical activity, and improved quality of life.

FUTURE PROSPECTUS

There is no doubt that it is necessary to continue to study the impact of curricula on the health of patients with cardiovascular risk. It is important to determine the minimum required time and intensity of training, to develop standardized for Ukraine teaching materials for patients. It is expedient to introduce a wide range of individual training programs into the practice of health care institutions aimed at improving the literacy of patients with high and very high cardiovascular risk.

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ORIGINAL ARTICLE
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GENETIC POLYMORPHISM ARG753GLN OF TLR-2, LEU412PHE OF TLR-3, ASP299GLY OF TLR-4 IN PATIENTS WITH INFLUENZA AND INFLUENZA-ASSOCIATED PNEUMONIA

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ABSTRACT

The aim of the research is to study the prevalence and to determine the prognostic significance of polymorphism ARG753GLN of the TLR-2 gene, Leu412Phe of TLR-3, Asp299Gly of TLR-4 in influenza.

Materials and methods: 112 patients with influenza were examined (63 patients with uncomplicated course and 49 with influenza-associated pneumonia). The genotyping of the polymorphic site of ARG753GLN of the TLR-2 gene, Asp299Gly of the TLR-4 gene, and Leu412Phe of the TLR-3 gene was carried out by polymerase chain reaction using oligonucleotide primers.

Results: It has found that the prevalence of the mutant allele 299Gly of TLR-4 in patients with uncomplicated influenza is 6.4 %, with influenza- associated pneumonia – 7.1 %, which exceeds the population control indicators by 3.8-4.3 times (1.7 %, $p<0.05$). Mutant allele 412Phe of TLR-3 is significantly more common in patients with influenza-associated pneumonia (42.9%), as compared with uncomplicated influenza (24.6%, $p<0.01$) and healthy people (30.0%, $p<0.05$). The increased risk of influenza development is associated with the Asp/Gly genotype of TLR-4 (OR=4.22) and combination of mutant genotypes Leu/Phe and Phe/Phe of TLR-3 with Asp/Gly of TLR-4 and Arg/Gln of TLR-2 (OR=15.0); influenza-associated pneumonia – with genotype Phe/Phe of TLR-3 (OR=4.5).

Conclusions: It has been found out that among patients with influenza and influenza-associated pneumonia, the mutant allele 299Gly of TLR-4 and combinations of polymorphisms Arg753Gln of TLR-2, Leu412Phe of TLR-3, Asp299Gly of TLR-4 are detected reliably more often. The frequency of the mutant allele 412Phe of TLR-3 is higher among patients with influenza-associated pneumonia. Markers of increased risk of influenza are 299Gly allele and genotype Asp/Gly of TLR-4 and the combination of mutant genotypes Leu/Phe and Phe/Phe of TLR-3 with Asp/Gly of TLR-4 and Arg/Gln of TLR-2; for influenza-associated pneumonia – allele 412Phe and genotype Phe/Phe of TLR-3.

KEY WORDS: influenza, influenza-associated pneumonia, Arg753Gln polymorphism of the TLR-2 gene, Asp299Gly polymorphism of the TLR-4 gene, Leu412Phe polymorphism of the TLR-3 gene, genotype, allele

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INTRODUCTION

Influenza and other acute respiratory infections are the most large-scale diseases that occupy the leading place in the structure of infectious diseases and constitute up to 80-90% of all cases of infectious pathology [1]. According to WHO estimates, each year, influenza globally afflicts up to 500 million people, 2 million of whom die. The highest number of fatal cases in influenza is due to complications, the leading place (80-90%) among which belongs to pneumonia [2], that develops mainly in patients at risk (pregnant women, patients with diabetes, obesity, chronic diseases of the lungs and heart, people of senior age groups, etc.) [3, 4]. However, according to WHO, 30% of patients who were previously considered healthy may also have severe and complicated influenza, which necessitates further study of factors affecting the course and sequelae of the disease [4].

It is known that the individual susceptibility of the body to infections is determined by pathogenicity of a microorganism, factors of the environment and the state of the immune system. It is the innate immune system that plays a crucial role in protecting the body from pathogens whose recognition is based on the Toll-like (TLR) receptor family. Excitation of TLR during the infection of the respiratory tract leads to the activation of genes involved in the regulation of the inflammatory process, the innate mechanisms of protection against infectious agents, acquired immunity [5]. The genes that control the type of immune response, the sensitivity/resistance to the influenza, the propensity to various forms of the course and development of complications, include primarily the TLR-2, TLR-3, and TLR-4 genes [6]. These receptors are involved in the recognition of the viral structural proteins and ligands of gram-positive and gram-negative bacteria (TLR-2 and TLR-4), as well as of dlRNA, which is the product of replication and transcription of RNA- and DNA-genomic viruses (TLR-3) [7-9].

Recent studies have shown that the TLR dysfunction, associated with the polymorphism of their genes, leads to the disturbance in the recognition of pathogens and imbalance in the functioning of the congenital immunity system, thus increasing the sensitivity to infections and determining the

severity of the course of the infectious process, which acquires the nature of the systemic inflammatory response [10].

Taking into account the data of scientific literature, which indicates that susceptibility to infectious agents is genetically determined, the search for markers associated with the development of influenza and its complications among alleles of the TLR genes is a relevant task, the solution of which will allow us to predict the severity of the course and consequences of this pathology.

THE AIM

The aim of the research is to examine the prevalence and determine the prognostic significance of polymorphism Arg753Gln of the TLR-2 gene, Leu412Phe of the TLR-3 gene, Asp299Gly of the TLR-4 gene in influenza.

MATERIALS AND METHODS

In order to achieve this aim, 112 patients were examined, out of them – 63 with uncomplicated course of the disease and 49 with influenza-associated pneumonia. The patients were treated at the regional clinical infectious disease hospital (Poltava, Ukraine), in the epidemiologic season of 2009-2014, among them 55 women (49.1%), 57 men (50.9%), aged from 17 to 61 years (mean age 34.4 ± 1.38). Most of the examined patients (76.8%) are young and middle-aged people. The population control group to study the prevalence of the Arg753Gln polymorphism of the TLR-2 gene and Asp299Gly of TLR-4 was 90, for the Leu412Phe of TLR-3 – 80 apparently healthy residents of Poltava region.

The study included patients of both sexes, aged ≥18 years with laboratory- diagnosed influenza, who did not belong to the risk groups of the complications of this disease (pregnant women, patients with diabetes mellitus, obesity, chronic diseases of the lungs and heart, liver, kidneys, as well as persons of elderly age groups, etc.). Exclusion criteria were age <18 years, negative results of laboratory tests (serological and molecular biology) for influenza, the presence of risk factors for the development of complications.

All studies were conducted after the signing of the informed consent by patients. The study was approved by the Commission on Ethical Issues and Bioethics of the Higher State Educational Establishment of Ukraine «Ukrainian Medical Stomatological Academy» (Approval No. 350).

Influenza was diagnosed on the basis of characteristic clinical and epidemiological data and confirmed by the results of laboratory tests (serological and molecular biology). The A/H1N1 virus has been isolated in 39.3%, A/H3N2 – in 35.7%, A/H2N2 – in 0.9%, B – in 21.4%. Mixed-forms were represented by the combination of antigenic variants of influenza A viruses (H1N1 + H3N2) (1.8%), A/H1N1 and B (0.9%) viruses that were registered in patients with influenza-associated pneumonia.

The diagnosis of pneumonia was verified according to the recommendations of the European Respiratory Society (ERS, 2011) and the Order of Ministry of Public Health of Ukraine No. 128 as of March 19, 2007 «On Approval of Clinical Protocols for the Provision of Medical Service in the Specialty «Pulmonology».

To determine polymorphism ARG753GLN of TLR-2, Asp299Gly of TLR-4, and Leu412Phe of TLR-3, we collected the samples of patients peripheral blood (2 ml) in the vials with ethylene diamine tetraacetic acid (EDTA) which were stored at -20°C and transported for testing in the laboratory (Research Institute of Genetic and Immunological Foundations of Pathology and Pharmacogenetics, «Ukrainian Medical Stomatological Academy» Poltava, Ukraine). Genomic DNA was isolated using the «Kit for DNA/RNA isolation from serum or plasma» (LitTech, Russia).

Polymorphic area Arg753Gln of the TLR-2 gene and Asp299Gly of TLR-4 were amplified at the «Tertsik» amplifier («DNA-technology», Russia), by PCR using specific oligonucleotide primers for the TLR-2 gene: 753TLR2F, 5'-GAGTGGTGCAAGTATGAACTGGA-3'; and 753TLR2R, 5'-TCCCAACTAGACAAAGACTGGTCT-3', for TLR-4: 299TLR4F, 5'-GATTAGCATACTTAGACTACTACCTCCATG-3'; and 299TLR4R, 5'-GATCAACTTCTGAAAAAGCATTCCCAC-3'.

The amplification programs for the TLR-4 and TLR-2 genes included: initial denaturation at 95°C for 5 minutes, 32 cycles: 95°C for 30 seconds, ignition at 58°C, 60 seconds, chain elongation at 72°C, 60 seconds, the program was completed with final elongation at 72°C, 3 min.

To identify the alleles of the TLR-4 gene, we applied restriction analysis of amplicons using restriction endonuclease Bsp19 (SibEnzim, Russia), for TLR-2 – endonuclease restriction Pst I (SibEnzim, Russia) at 37°C. As a result of the restriction, fragments of 263 bp and 222 bp were obtained for the Asp299Gly polymorphism and 300 bp for Arg753Gln.

To determine the alleles of the Leu412Phe polymorphic site of the TLR-3, genomic DNA gene was isolated from peripheral blood leukocytes using the reagent kit of «DNA-EXPRESS-blood» (LitTech, Russia). The amplification program for the TLR-3 gene included initial denaturation at 93°C for 60 seconds, 35 cycles: 93°10 seconds, ignition at a specific temperature of 64°C for each pair of primers, 10 seconds, chain elongation at 72°C, 20 seconds, final elongation at 72°C, 60 seconds.

The breakdown products of the polymorphic site of the TLR-4, TLR-2 genes were detected by electrophoresis in the 3% agarose gel in 1 TBE (50 mM tris-H_3PO and 2 mM EDTA, PH = 8.0), for 2 hours at a voltage of 2 V 1 cm of gel; TLR-3 – in 1 x tris-acetate (TAE) buffer, prepared from 50 x TAE buffer (0.04M tris-acetate, 0.002M EDTA, pH = 8.3) at a voltage of 10-15 V per 1 cm of gel. Gels were stained with 1% solution of ethidium bromide with subsequent visualization of the results in UV light.

In mathematical processing of the data, we used the software «Statistica for Windows 7.0» (StatSoft Inc, USA) and MS Excel. The distribution of investigated polymorphic genotypes was checked for compliance with the Hardy-Weinberg equilibrium using the χ^2 criterion. Comparison of the frequencies of genotypes and alleles between the studied groups was conducted using Fisher's exact test. The differences were considered reliable at $p<0.05$. The relative risk of disease and complications were evaluated using OR

Table 1. Distribution in frequencies of genotypes and alleles of the Leu412Phe polymorphism of the TLR-3 gene among patients with influenza, influenza-associated pneumonia and healthy subjects, abs. number (%)

Genotype and alleles	Healthy subjects n = 80	Groups of patients		F p≤	OR (95 % CI)
		uncomplicated influenza n = 63	influenza-associated pneumonia n = 49		
Leu/Leu	36 (45.0)	35 (55.5)	16 (32.7)	0.2403 a 0.1973 b 0.0216 d	1.53 (0.79-2.97) a 0.59 (0.28-1.24) b 0.39 (0.18-0.84) d
Leu/Phe	40 (50.0)	25 (39.7)	24 (48.9)	0.2399 a 0.9999 b 0.3437 d	0.66 (0.34-1.28) a 0.96 (0.47-1.95) b 1.46 (0.69-3.1) d
Phe/Phe	4 (5.0)	3 (4.8)	9 (18.4)	1.00 a 0.0309 b* 0.0299 d*	0.95 (0.2-4.41) a 4.28 (1.24-14.75) b 4.5 (1.15-17.65) d
Leu	112 (70.0)	95 (75.4)	56 (57.1)	0.3519 a 0.0434 b 0.0042 d	1.31 (0.77-2.23) a 0.57 (0.34-0.96) b 0.44 (0.25-0.77) d
Phe	48 (30.0)	31 (24.6)	42 (42.9)	0.3519 a 0.0434 b* 0.0042 d*	0.76 (0.45 – 1.29) a 1.75 (1.04-2.95) b 2.3 (1.3-4.06) d

Note: here and in Table 1, 2, p is the level of significance obtained by Fischer's exact test for differences in the frequencies of genotypes and alleles between: a – healthy subjects and patients with uncomplicated influenza; b – healthy subjects and patients with influenza-associated pneumonia; d – patients with uncomplicated influenza and influenza-associated pneumonia.

rate with defining 95% confidence interval (CI). The indicator OR=1 was considered as a lack of association; OR>1 – as a positive association ("predisposition"), OR<1 – as a negative association of allele or genotype with the disease.

RESULTS AND DISCUSSION

As a result of the molecular-genetic examination of 112 patients with influenza, the following genotypes of the studied TLRs were obtained: TLR-2 – Gln753Gln, Arg753Gln; TLR-3 – Leu412Leu, Leu412Phe, Phe412Phe; TLR-4 – Asp299Asp, Asp299Gly. The distribution of genotypes corresponded to the expected Hardy-Weinberg equilibrium in the groups of patients with influenza, influenza-associated pneumonia and healthy people for all investigated polymorphic loci.

In analyzing the results of the study, it was found that among the patients with influenza, the Leu412Phe polymorphism of the TLR-3 gene, Asp299Gly of TLR-4, as well as their combination with Arg753Gln of TLR-2 were determined more often, as compared with apparently healthy ones. Distribution in frequencies of genotypes and alleles of the Leu412Phe polymorphism of TLR-3 among the examined groups are presented in Table 1.

As can be observed from the data presented in Table 1, the prevalence of the mutant homozygous genotype Phe/Phe of TLR-3 and allele 412Phe was significantly higher among patients with influenza-associated pneumonia by 3.7 and 1.4 times (p=0.03 and p=0.04), as compared with healthy subjects and by 3.8 and 1.7 times (p=0.02 and p=0.004) – as compared to patients with influenza. The presence of the 412Phe mutant allele in the genome of patients with influenza and homozygous genotype Phe/Phe by 2.3 and 4.5 times increases the risk of influenza-associated pneumonia (OR=2.3; 95% CI: 1.3-4.06 and OR=4.5; 95% CI: 1.15-17, 65, respectively).

A comparative analysis of the frequencies in genotypes and alleles of the Asp299Gly polymorphism of the TLR-4 gene between the examined groups of patients and the healthy subjects is presented in Table 2.

Regarding the Asp299Gly polymorphism of the TLR-4 gene, it has been found that frequency of the heterozygous genotype Asp/Gly and the mutant allele 299Gly is higher among patients with influenza by 3.8 (p<0.05), with influenza-associated pneumonia by 4.3 times (p=0.03), as compared to healthy subjects. In carriers of the 299Gly allele of the TLR-4 gene, there was a higher risk of influenza by 4.0 times (OR=4.0; 95% CI: 1.04-15.39) than in those with the Asp299Asp genotype.

When comparing the frequencies of genotype and alleles of the Arg753Gln polymorphism of TLR-2, there were no statistically significant differences between the examined groups. Frequency of the heterozygous genotype Arg/Gln of TLR-2 among the patients with influenza was 4.8%, influenza-associated pneumonia – 6.1%, healthy – 3.3% (p>0.05), and the 753Arg alleles – 2.4%, 3.1% and 1.7% (p>0.05) respectively.

Table 2. Distribution of genotypes and alleles of the Asp299Gly polymorphism of the TLR-4 gene among patients with influenza, influenza-associated pneumonia and healthy subjects, abs. number (%)

Genotype and alleles	Healthy subjects n=90	Groups of patients		p (F)	OR (95 % CI)
		uncomplicated influenza n=63	influenza-associated pneumonia n=49		
Asp/Asp	87 (96.7)	55 (87.3)	42 (85.7)	0.0516 a 0.0334 b 0.9999 d	0.24 (0.06-0.93) a 0.21 (0.05-0.84) b 0.87 (0.29-2.6) d
Asp/Gly	3 (3.3)	8 (12.7)	7 (14.3)	0.0516 a* 0.0324 b* 0.9999 d	4.22 (1.07-16.59) a 4.95 (1.22-20.13) b 1.15 (0.38-3.41) d
Gly/Gly	0 (0.0)	0 (0.0)	0 (0.0)	0	0
Asp	177 (98.3)	118 (93.6)	91 (92.9)	0.0561 a 0.0367 b 0.9999 d	0.25 (0.06-0.96) a 0.22 (0.06-0.87) b 0.88 (0.31-2.52) d
Gly	3 (1.7)	8 (6.4)	7 (7.1)	0.0561 a* 0.0367 b* 0.9999 d	4 (1.04-15.39) a 4.54 (1.15-17.97) b 1.13 (0.4-3.24) d

The absence of mutant homozygous genotypes Arg753Arg of TLR-2 and Gly299Gly of TLR-4 was noted for both patients with influenza and healthy subjects, which corresponds to the data of scientific literature about the low frequency of their prevalence in the population [11, 12].

Combinations of mutant genotypes of TLR-2, TLR-3, TLR-4 was only registered in patients with influenza (11.1%, p<0.01) and influenza-associated pneumonia (14.3%, p<0.003), and it was not detected in healthy subjects. Most (80.0%) combinations included polymorphically modified genotypes of TLR-3. The most common, both among patients with influenza and influenza-associated pneumonia, was the combination of the heterozygous genotype Leu/Phe of TLR-3 with Asp/Gly of TLR-4 (6.3% and 10.2% respectively).

It has been established that the presence of mutant genotypes of TLR-3 in the genome in combination with TLR-2 and TLR-4 by 15.0 times (OR=15.0; 95% CI: 1.83-286.93) increases the risk of influenza development in the carriers of these mutations.

Thus, we have proved that the presence of PheLeu412 polymorphisms of the TLR-3 gene, Asp299Gly of TLR 4 and their combinations with Arg753Gln of TLR-2 make it possible to predict the risk for development of influenza and influenza-associated pneumonia. Previous studies have shown that polymorphism of TLR genes causes the predisposition to a variety of diseases, as well as the severity of their course. Hence, at present, the Asp299Gly polymorphism of the TLR-4 gene is associated with the development of hematogenous osteomyelitis, systemic candidiasis, bronchial asthma, sepsis, caused by gram-negative bacteria, respiratory viral infections in children [13-17].

The association between Arg753Gln of TLR-2 has been established with increased risk for development of tuberculosis, acute rheumatic fever in children, septic shock, caused by gram-positive bacteria, CMV-infections in patients after liver transplantation [18-21]. In the study by Nachtigall I. et al. [22], the connection between the Arg753Gln polymorphism of the TLR-2 gene and the Asp299Gly of the TLR-4 gene with rapid progression and severe sepsis has been proven.

A number of scientific studies link the SNP Leu412Phe polymorphism of TLR-3 with the development of subacute sclerosing panencephalitis in the cortex, myocarditis and dilated cardiomyopathy in enterovirus infection, severe course of atypical pneumonia with the development of GERD, induced by the coronavirus [23-25].

Thus, active research of genetic variability of TLR in the last decade produces evidence that polymorphism of single nucleotides through the formation of specific gene alleles makes an important contribution to the individual features of development of protective reactions, as well as susceptibility to a variety of diseases.

CONCLUSIONS

1. The frequency of the Asp/Gly heterozygous genotype of TLR-4 in patients with influenza constituted 12.7%, with influenza-associated pneumonia – 14.3%, which exceeded the indicators of population control by 3.8-4.3 times (3.3 %, p<0.05).
2. The homozygous genotype Phe/Phe of TLR-3 in patients with influenza-associated pneumonia was determined with the frequency of 18.4 %, which exceeded the rates of patients with uncomplicated influenza (4.8%, p=0.02) and healthy subjects (5.0%, p=0.03).
3. The combination of mutant genotypes of TLR-2, TLR-3, TLR-4 was not detected in healthy subjects and was determined in patients with influenza and influenza-associated pneumonia with the frequency from 11.1% to 14.3% (p<0.05).
4. The presence of polymorphically modified genotypes of TLR-4, TLR-3 and their combinations with TLR-2 allows

us to predict the risk for development of influenza and influenza-associated pneumonia. Markers of increased risk of influenza are the 299Gly allele and the Asp/Gly genotype of TLR-4 (OR=4.0 and OR=4.22, respectively) and the combination of mutant genotypes Leu/Phe and Phe/Phe of TLR-3 with Asp/Gly of TLR-4 and Arg/Gln of TLR-2 (OR=15.0); influenza-associated pneumonia – the 412Phe allele and the Phe/Phe genotype of TLR-3 (OR=2.3 and OR=4.5, respectively).

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ORIGINAL ARTICLE
PRACA ORYGINALNA

COMPARATIVE ANALYSIS OF INTRAOPERATIVE BLOOD LOSS DURING THE CLASSICAL CESAREAN SECTION DE SCRIBED BY M. STARK AND THE MODIFIED CESAREAN SECTION

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ABSTRACT

Introduction: According to the WHO, obstetric bleeding keeps a leading position among the top three causes of maternal mortality. The incidence of abnormal blood loss (BL) varies widely from 1.5% to 22%, and the incidence of acute blood loss reaches up to 1,7%, with the variation from 0% to 4%. Every year, this complication causes death in 128 women that amounts to 1.7% per 1,000 deliveries

The aim of this study is a comparative analysis of intraoperative blood loss during the classical cesarean section described by M. Stark and modified cesarean section was performed.

Materials and metods: The study has been conducted on the basis of the Obstetrics department of the Kherson regional clinical hospital. Patients were selected according to the type of surgery (the classical technique described by M. Stark or the modified method) for the period from 2015 to 2018. The formation of the clinical groups was performed in accordance with the retrospective data retrieved from the labor and delivery records of 205 patients, who delivered via cesarean section. The comparative estimation of intraoperative blood loss volumes was carried out using a direct (gravimetric) method.

Results: The proposed modification of abdominal delivery is based on the rational teamwork of a surgeon and an assistant, with the modernization of the surgical stages allowed halving the surgery duration as compared to the classical cesarean section technique introduced by M. Stark. And the improved surgical technique of abdominal delivery contributes to the reduction in the volume of intraoperative blood loss by 200 ml ($p < 0,001$).

Conclusions: Modified cesarean section allows avoiding massive obstetric hemorrhage, thereby creating an additional reserve for improving the safety of the operative delivery in general.

KEY WORDS: cesarean section, intraoperative blood loss, a technique, modification

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INTRODUCTION

According to the World Health Organization, obstetrical bleeding (OB) remains unchanged as one of the main causes of maternal mortality. The incidence of abnormal blood loss (BL) varies widely from 1.5% to 22%, and the incidence of acute blood loss reaches up to 1.7%, with the variation from 0% to 4%. During cesarean section, blood loss of more than 1000 ml occurs 14 times more often than during vaginal delivery. Every year, this complication causes death in 128 women that amounts to 1.7% per 1,000 deliveries [1, 2, 3, 4]. This is uterine atony that may be caused by the disadvantages of the used surgical technique and is the main reason for the hysterectomy that is done in almost half of all cases during abdominal delivery [3, 5, 6]. The method of abdominal delivery, which was developed by a group of physicians headed by M. Stark, made the c-section more technically-available to operators. One of the goals of this method is to exclude all unnecessary actions so that surgery was performed faster and with less blood loss. However, the development of medicine is on the go all time and thus the technical aspects of surgery should be constantly improved. To date, the basic principles of surgical techniques differ from the generally accepted ideas to a certain extent and tend towards minimal invasiveness at all surgical stages. The above-mentioned data reflect the urgency of the problem of OB during cesarean section what is the reason to improve the surgical technique for abdominal delivery, develop and implement new techniques for reducing blood loss during surgery, reduce the incidence of hysterectomies, and maintain women's reproductive health and save their lives.

THE AIM

To carry out a comparative analysis of intraoperative blood loss during the classical cesarean section described by M. Stark and a modified method of cesarean section to prevent massive obstetric hemorrhage and improve maternal outcomes.

MATERIALS AND METHODS

The study has been conducted on the basis of the Obstetrics department of the Kherson regional clinical hospital. Patients were selected according to the type of surgery (the classical technique described by M. Stark or the modified method) for the period from 2015 to 2018. The formation

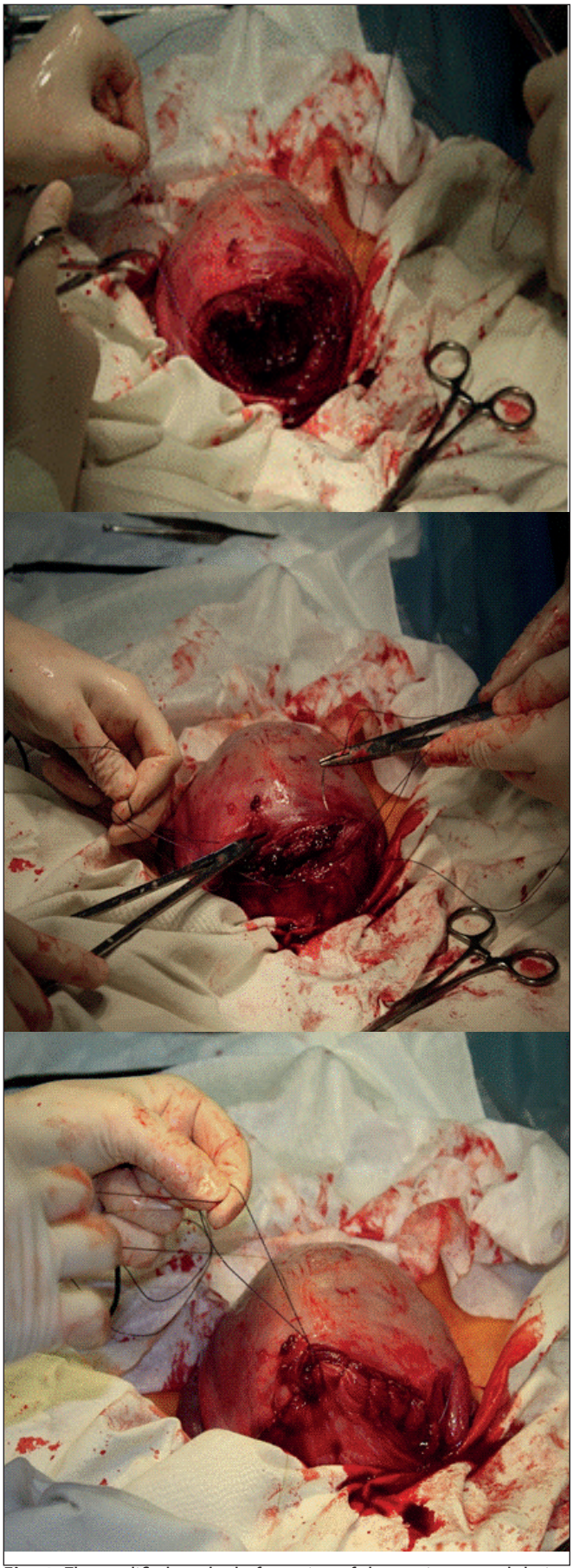

Fig. 1. The modified method of suturing of the uterine wound during cesarean section.

of the clinical groups was performed in accordance with the retrospective data retrieved from the labor and delivery records of 205 patients, who delivered via cesarean section. The I clinical group included 108 patients, who underwent a cesarean section performed in accordance with the offered modified method [7, 8]. The comparative group (II clinical group) included 97 pregnant women, who underwent the classical cesarean section described by M. Stark.

The differences between the given cesarean section technique and the modified method are as follows:

1. Unlike the Joel-Cohen incision, during the modified method of cesarean section, a laparotomy is performed just above the womb, on the lower skin fold, and the cut is 10-12 cm long.
2. In contrast to the cesarean section technique described by M. Stark, the dissection of the fascia is performed without scissors. To form access to the abdominal cavity, a cut in the midline of the fascia with the length of up to 2 cm is made, the peritoneum is seized with an index finger and all the layers of the anterior wall are stretched by blunt dissection by two surgeons simultaneously.
3. In case of a repeat cesarean section, the uterine incision is performed above the previous scar.
4. There is no routine instrumental curetting of the uterine cavity.
5. The fundamental of the proposed method is based on the teamwork of a surgeon and an assistant. The main differentiating feature of this method of the cesarean section consists in the simultaneous suturing of the uterus wound by two operators, starting from the corners of the wound edges with a continuous Vicryl suture with fixation forceps on each end of two surgical sutures (Fig. 1).
6. The fascia and skin are sutured for an analogy.

All women went through general clinical, physical, laboratory, and instrumental examinations in accordance with the industry standards [1, 8].

The comparative estimation of intraoperative blood loss volumes was carried out using a direct (gravimetric) method [9]. The desired value was determined by the difference in mass of dry and blood-impregnated sponges, beads, diapers, dressing gowns, and the volume of the blood that was collected in measuring containers during surgery and calculated by using the formula of Libov:

The volume of blood loss = B / 2 * k, where

B / 2 - total weight of the material impregnated with blood,

k = 15% for blood loss <1000 ml,

k = 30% for blood loss> 1000 ml.

The amniotic fluid volume was estimated by determining the amniotic index, which is the sum of the largest vertical water pockets in the four quadrants, and the results were compared with the normative values.

The analysis of the investigated clinical and anamnestic and preoperative factors indicates that there are no statistically significant differences (p> 0,05%) in the patients of both clinical groups (Table I). There were no cases of a low lying placenta, placenta previa, and abnormally invasive placenta observed in both groups.

Table I. Comparative characteristics of the investigated preoperative predictors in pregnant women in two clinical groups (n = 205)

Index	Primary group (n=108)		Comparative group (n=97)		Σ (n=205) (%)	p
	n (%)	Medium (M ± m)	n (%)	Medium (M ± m)		
Age profile (years old)	108	29,97±5,59	97	28,71±5,65	29,38±5,64	0,11
Weight (kg)	108	80,7±18,88	97	77,58±13,74	79,22±16,68	0,181
Parity rate	108	1,5±0,73	97	1,36±0,58	1,44±0,67	0,124
Gestation age (weeks)	108	37±3,84	97	37±4,5	37±4,06	1
Uterine scar after cesarean section	40 (37,0)	1,33±0,67	30 (30,9)	1,21±0,77	70 (34,15)	0,379
Hemoglobin level at the preoperational stage (g/l)	108	112,56±13,68	97	113,89±14,91	113,22±14,28	0,518
Hematocrit volume at the preoperative stage (%)	108	32,76±4,04	97	32,86±5,21	32,81±4,57	0,899
Platelet count at the preoperative stage (x10^9/l)	108	224,49±53,7	97	220,12±62,9	222,39±58,16	0,623
Type of procedure (urgent)	34 (31,05)		43 (44,3)		77 (37,6)	0,062

A statistical analysis of the obtained results was carried out using the application R. The quantitative indicators, central tendency, and variability of the features were analyzed using the arithmetical mean value and the error of the mean value calculation. The qualitative indicators were measured in absolute and relative (percentage) values. The probability of differences between parametric characteristics in the appropriate groups was estimated using the Student's t-test and analysis of variance (ANOVA). During the calculations, the statistical significance level of 95% was used.

RESULTS AND DISCUSSION

Introduced by M. Stark in 1990, the cesarean section technique brought a transformational change into abdominal obstetrics and increased the safety of this surgical intervention as a whole. However, the maternal mortality rate associated with cesarean section (about 40 per 100,000 live births) remains 4 times higher than for all types of vaginal births (10 per 100,000 live births), and 8 times higher than for normal delivery (5 per 100,000 live births) [5].

The progressive increase in abdominal deliveries worldwide along with the lered health index of pregnant women makes it necessary to solve a number of problems associated with cold-technical stages of cesarean section to improve maternal and fetal outcomes.

In both clinical groups, cesarean section was performed by experienced physicians whose surgical skills correspond to the highest qualification category and do not affect the quality of any of the investigated parameters (Table II).

We believe that this is the rational teamwork of surgeons along with the modernization of the surgical stages that allowed halving the surgery duration as compared to the classical cesarean section technique introduced by M. Stark. This was conditioned by the use of the modified technique for accessing the abdominal cavity and suturing the wound on the uterus and the layers of the anterior abdominal wall in accordance with the proposed method. The minimum surgery duration was observed in the I clinical study group, where it was 9 minutes, the maximum one was 43 minutes, and the medium one was 21.63 ± 7.97 minutes. In the II clinical group, the minimum surgery duration was 25 minutes, the maximum one was 1 hour 30 minutes, and the medium one was 47.26 ± 13.62 minutes, the difference was significant ($p < 0.01$).

The reduction in the duration of abdominal deliveries has a number of significant benefits, and above all, has a beneficial effect on reducing intraoperative blood loss. This is because, by optimizing the surgical stages (in particular, the refusal to access the abdominal cavity by sharp dissection), it allows performing sparing dissection of blood vessels and maintaining the appropriate architectonics, thereby minimizing the need in the further hemostasis process; the exteriorization of the uterus improves the visualization of the wound, reducing the need for using forceps that cause additional iatrogenic damage to tissue; the refusal to perform routine instrumental curettage eliminates the probability of bleeding from the placental area of the uterus. We advise draining blood from the cavity in a more secure way by using a sponge. The modified technique of suturing of the womb on the uterus described above is the key stage of the overall duration of the cesarean section and the main method to minimize inoperative blood loss. By applying this method, the main source of bleeding is eliminated on the 3d or 4th minute from the beginning of laparotomy. The incorporation of new types of energy, namely argon-plasma coagulation, into the process is an effective additional method of high-frequency electrosurgery for reducing bleeding; however, it has a number of limitations and is used for performing primary homeostasis as the coagulation depth is no more than 3 mm.

We believe that the key element for reducing intraoperative blood loss is the quality of the surgical technique used for suturing the uterus. Since the suturing process begins from two corners of

Table II. Comparative analysis of the intraoperative phase during the Stark's classical cesarean section and modified cesarean section (n = 205)

Index	Primary group (n=108)		Comparative group (n=97)		Range	Σ (n=205) (%)	p
	n (%)	Medium (M ± m)	n (%)	Medium (M ± m)			
Surgery duration (minutes)	108	21,63±7,97	97	47,26±13,62	9 – 90	33,76±16,89	<0,001
Time before a baby is removed(minutes)	108	3,78±1,77	97	7,67±4,05	1 - 20	5,62±3,63	<0,001
Body temperature (t^0 C)	108	36,6±0,11	97	36,5±0,15	36,4 – 36,8	36,6±0,78	>0,05
Use of carbetocine	15	13,8%	30	30,9%	45	21,9%	0,011
Hemotransfusion	0	0%	5	5,2%	5	2,4%	0,022
Hysterectomy	0	0	2	2,06%	2	0,97	1

Table III. Blood loss volume calculated during cesarean section in the clinical groups (n=205) (M ± m)

Clinical group	Blood loss volumes, ml					
	n	Medium	Standard average error	Standard deviation	Range	95% Confidence interval
I clinical group (primary) n - 108	108	322,48	7	72,72	250 - 850	308,77 - 336,2
II clinical group (comparative) n - 97	97	528,27	17,92	176,49	350 - 1600	493,14 - 563,39
Σ	205	419,85	11,7	167,45	250 - 1600	396,93 - 442,78
p				<0,001		
d Cohen				1,55 95% CI: 1,5 - 1,61		

the wound simultaneously, the risk of massive hematoma is minimized taking into account the topography of the vessels, and the time during which the wound remains open is reduced by 50%.

In the course of the investigation, the intraoperative blood loss volumes were estimated by using the direct method which requires the use of suction bags. We believe that since there is no credible alternative, the gravimetric method is the most informative one in estimating the amount of blood loss; however, it has some disadvantages. Technical difficulties arose when blood loss was calculated in patients with excessive body weight. In addition, during cesarean section, the amniotic fluid outflows, and its volumes vary from one individual to another and thus greatly reduce the objectivity of this method. However, according to the amniotic index data, the volumes of amniotic fluid in both clinical groups were medium and did not affect the results of the investigation.

The blood loss volume in the I clinical group was significantly lower and amounted to 322.48 ± 72.72 ml versus 528.27 ± 176.49 ml in the II clinical group, the difference was statistically significant (p^3 0.001, 95% CI: 1, 5 - 1.61). In addition, 32 (29.6%) patients from the main group had a minimum volume of blood loss, which was 250 ml, and this volume can be put equal to the average volume of blood lost during vaginal birth. The maximum intraoperative blood loss in 5 (4.6%) women in labor from the I clinical group was 850 ml, which constituted approximately 0.9% of their body weight and 17% of their blood volume and looked very like pathological OB. Instead, 12 (12.4%) women from the II clinical group, who underwent a classical cesarean section, had blood loss of 1200-600 ml, which constituted about 1.6% of their body weight and more than one third of their blood volume, and this is defined as a state of massive obstetric hemorrhage (MOH), which, in 5 (5.2%, $p < 0.022$) cases, required intraoperative blood transfusion and, in 2 (2.06%) cases, became a reason for a hysterectomy. However, this difference was statistically insignificant. In addition, the minimization of the time required for suturing of the uterus along with the ensured fast adequate hemostasis in the primary group almost halved the need to use the expensive drug, carbetocin, which was used only in 13.8% of cases in the I group by contrast to 30.9% of cases in the comparative group ($p < 0.011$) that positively affects the cost of abdominal delivery.

Since the indications for cesarean delivery were similar in two investigated groups, we can assume that both a well-organized, integrated approach to abdominal delivery and an optimized surgical technique increase the effectiveness of the prevention of the MOH and account for the elimination of blood transfusions and hysterectomies in the primary group. However, when the data regarding the volume of blood loss were analyzed, a controversial issue was raised. According to the Order of the Ministry of Health of Ukraine No. 205 dated 24.03.14. during vaginal delivery, blood loss of more than 500 ml is defined as pathological, then how is it possible that during cesarean section,

when women in labor have a massive wound surface, pathological blood loss is the one which volume exceeds 1000 ml?

In addition, the modified cesarean section has an influence over some prenatal outcomes. The reduction in the surgery duration at the stage of entering the abdominal cavity contributes to the reduction in the time needed for removing a baby in two times what is especially important during an urgent cesarean section in case of fetal distress, prolapsed umbilical cord, or placental abruption when the baby has a few minutes left. Due to the use of the enhanced access to the uterus, in the I clinical group, the fetus was removed on an average on 4 minutes earlier ($p<0,001$) than in the comparative group what improved the outcomes for the newborn during the early neonatal period.

Reduction in the duration of cesarean section makes it possible to avoid hypothermia in women in labor. Unfortunately, this phenomenon is very underestimated by experts. Hypothermia is in itself a dangerous phenomenon that can become a lethal threat even to a physically healthy person, not to mention a pregnant woman and fetus. Scientists have shown that body temperature is reduced by 0.5 ^{0}C for each additional hour of surgery, and only few maternity hospitals in Ukraine are currently equipped with heated tables or electric blankets. On the basis of the undertaken study, all the women in labor avoided hypothermia, and a slightly lower temperature was observed in the patients from the comparative group, but the difference was insignificant ($p> 0.05$). In our opinion, this is an urgent problem that requires more in-depth research. The proposed method of the cesarean section also improves the mental well-being of a woman during surgery, optimizes the work of not only a surgical department but also an obstetric one in general.

CONCLUSIONS

The improved surgical technology of abdominal delivery contributes to the reduction in the volume of intraoperative blood loss by 200 ml ($p < 0,001$), which virtually eliminates the risk of massive obstetric hemorrhage and thus creates an additional reserve for improving the safety of operative delivery in general. The received results indicate the feasibility of the implementation and application of the modified method of cesarean section and thus create prospects for further research of the peculiarities of the intra-and postoperative period.

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ORIGINAL ARTICLE
PRACA ORYGINALNA

INNOVATIVE METHOD OF DIAGNOSTICS ABDOMINAL FORMS OF CRYPTORCHISM AT THE CHILDREN FOR PREVENTION OF INFERTILITY

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ABSTRACT

Introduction: Topicability of this problem is caused by well-spread of cryptorchism among children: from 2–3% at newborn boys in UK to 10–12% of newborn boys in the Post Soviet Union countries. Degenerative processes, occured in testicle could lead to the development of eunuchoidism, feminization, gynecomastia, infantilism. In the future, changes in seminiferous epithelium contribute to the development of male infertility, impotence and malignant tumors – seminoma, teratoblastoma.

The aim: To improve diagnosis for abdominal forms of cryptorchism at the children through implementation innovative methods in practice (laparoscopic diagnostics).

Materials and methods: For a period from 2014 to 2017 years were carried out 43 diagnostic laparoscopy of non palpated testicle syndrome. By age children were distributed into the following groups: up to 1 year -18 children, 1-2 years – 25 children.

Results: Analyzing results of our research there is no doubt that laparoscopy is one of the most reliable methods of diagnosis abdominal cryptorchism in children. This method allows both to determine location of a damaged testicle in the abdominal cavity, but also to assess its condition, developed further tactics of treatment.

Conclusions: Laparoscopic diagnosis abdominal forms of cryptorchism is the most reliable method in a comparison with computed tomography, ultrasound, radioisotope studies. Procedure of laparoscopic diagnosis could show not only location and condition of the testis, blood vessels and ductus deferens, but help to develop the further treatment tactics.

KEY WORDS: cryptorchism, testicles, reproductive system, eunuchoidism, feminization, diagnostic laparoscopy, children

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INTRODUCTION

Cryptorchism is a well-spread surgical disease of reproductive system. For example, according to different authors, prevalence this anomaly of sexual development is carried out from 2 - 3% at newborn boys in UK [1, 2] to 10 – 12% of newborn boys in the Post Soviet Union countries [3].

Degenerative processes, occured in neostarted up testicle could lead to violation of hormonal function with development of eunuchoidism, feminization, gynecomastia, infantilism. In the future, changes in seminiferous epithelium contribute to the development of male infertility, impotence and malignant tumors – seminoma, teratoblastoma [4]. Topicability of this problem is caused by well-spread of cryptorchism among children, outstanding issue of effective improvment a blood circulation of testicles during surgical correction of the given defect, lack of such methods of therapy, which would substantially reduce percentage of infertility in a reproductive period of men. There are many methods of diagnosis (ultrasound, selective testicular arteriography, computed tomography, radionuclide scintigraphy, pneumoperitoneography) [5]. However, it is still being a lot of unsolved problems towards treatment of cryptorchism at the children (surgical and conservative methods), which focused on the infringement of circulation and development of atrophy in relegated testicles. Absence of testicles in the inguinal canal in a case of cryptorchism, impossibility of its detection causing additional questions at the surgeon about further tactics. As a rule, further surgery is performed with element of uncertainty, because there is numerous variants: location of a testicle in the different parts of abdomen, agenesis of the testicle, presence of vestigial tissue in the gonads [6]. To define localization of testicle had been suggested variety methods of research: ultrasound, selective testicular arteriography, computed tomography, radionuclide scintigraphy, pneumoperitoneography et all. However, the most objective picture for location and testicle condition should give a diagnostic laparoscopy [7]. Its results could determine further tactics of treatment. With the help of this technique it should be defined location of the testicle, its condition. Diagnostic laparoscopy allows to forming common indications for open audit of the inguinal canal at the absence of significant data towards agenesis of the testicle.

Indications for diagnostic laparoscopy are some cases of non palpated testicle, an intra-abdominal cryptorchism, especially when results of other studies allow us to suspect location of a testicle in the abdominal cavity. Laparoscopic diagnosis abdominal forms of cryptorchism is the most reliable method of research, in comparison with computed tomography, radioisotope studies, ultrasound [8], because laparoscopy could determine not only location of the testicle, but their condition, state of testicle arteries, appendage,

deferent duct. Laparoscopic diagnostic allows, if necessary, to choose the optimum operational tactics.

Numerous international research works of scientists in this field of study were focused on the experiments on the rats and extrapolation of their results on the human organism. Demirci T. et all [9] study stress, obesity, and stress-obesity groups correlated with a significantly decreased in sperm concentration and motility in comparison with the control group, and significantly increased number of abnormal sperm compared to control. The study carried out by Mansour M. et all [10] of male rats were divided into control group (n = 15) and experimental group (n = 15). This is the first study to demonstrate concept of remote ischemic conditioning (RIC) in an animal model of testicular torsion.

El-Behery E.I. et all [11] suggested the possible protective role of orally administered ZnO NPs on testicular alterations in the STZ-induced diabetic group via steroidogenesis and spermatogenesis enhancement. In the study Mao C.F. et all [12] investigating whether the *Echinacea purpurea* ethanol extract (EE) encapsulated chitosan/silica nanoparticle (nano-EE) can enhance the amelioration of male infertility. Khalaji N. et all [13] was performed in order to uncover new aspects of Compact Florescent Lamps (CFLs) induced damages on the testicular tissue of rats and evaluating the effect of curcumin on testis of rats.

Numerous research works [14] focused on the histological structure of the testis in normal in control folic acid (FA) groups. The results of research Adelakun S.A. et all [15] revealed that the testis histoarchtecture showed normal cellular composition in their germinal epithelium, with sperm cells in the lumen and a normal interstitium.

In the experiment on rats, portal hypertension was simulated in an original way with the following study of the peculiarities of morphological changes in the internal structure of the kidneys and gonads in males as a manifestation of a violation of systemic hemodynamics [16]. Ivanova V.V. et all [17] show that sialoadenectomy in adult rats led (in 1-4 weeks) to a decrease in the nuclear and cytoplasmatic areas of Leydig cells, violation of the plasmalemma integrity, dilatation of perinuclear space and agranular endoplasmatic reticulum vesicles, and to destruction of the mitochondria.

The histopathological analysis of the testicle, liver and kidney tissues of the animals showed no difference between the groups, at the result of thymol and carvacrol administration decreased the oxidative damage and increased the antioxidant levels and improved the sperm quality parameters [18]. Boroja T. et all [19] suggest that S. hortensis may be a valuable source of dietary and pharmacologically important phenolic compounds, especially rosmarinic acid, in pharmaceutical and functional food formulations in order to maintain diseases caused by oxidative damage. Abdel-Wahab A. et all [20] aimed to determine the protective effects of co-administration of Quercetin (QT) or l-Carnitine (LC) against the oxidative stress in the reproductive system of intact male Albino rats.

Results of treatment surgical diseases of the testicle in children, at the present stage, are not satisfying children's surgeons with a high percentage of complications. Firstly – it is a high risk of development male infertility in the reproductive age [21]. Therefore, solving of this problem is an important step in a struggle for reproductive health of nation and preservation of a full-fledged family [22-23].

The data presented at work of Dumont L. et all [24] will help to improve apoptotic and autophagic understanding during the first spermatogenic wave. Moreover, findings illustrate for the first time that, using finely-tuned experimental conditions, a testicular in vitro culture combined with proteomic technologies may significantly facilitate the study of cryopreservation procedures and in vitro culture evaluations. On the manuscript of Rajanahally S. et all [25] were studied 30 pertained to marijuana and male infertility, 36 discussed cannabis and male sexual health/hormones, and 25 explored the relationship between marijuana and urologic neoplasms. With respect to male factor fertility using semen parameters as a surrogate, cannabinoids likely play an inhibitory role.

In the present study Meng C. et all [26] found that L3MBTL2 was most highly expressed in pachytene spermatocytes within the testis. Germ cell-specific ablation of L3mbtl2 in the testis led to increased abnormal spermatozoa, progressive decrease of sperm counts and premature testicular failure in mice.

El Zowalaty AE. et all [27] demonstrate novel roles of seipin in spermatid chromatin integrity, acrosome formation, and mitochondrial activity. Increased spermatid apoptosis, increased chromocenter fragmentation, defective chromatin condensation, abnormal acrosome formation, and defective mitochondrial activity contributed to decreased sperm production and defective sperm that resulted in Bscl2-/- male infertility.

Fode M. et all [28] demonstated, that low intensity extracorporal shock wave therapy (Li-ESWT) may induce tissue regeneration, neo-angiogenesis and improve endothelial function. This has shown promise in the treatment of erectile dysfunction (ED). Li-ESWT has shown promise in pelvic pain and its effects on testicles have been preliminarily investigated in preclinical studies.

At the work of Rocca M.S. et all [29] was shown that sperm telomere length (STL) is associated with standard semen quality parameters and it is significantly associated with levels of DNA fragmentation and sperm protamination.

Telomeres are fundamental for genome integrity. Recent studies have demonstrated that STL increases with age and men with oligozoospermia have shorter sperm telomeres than normozoospermic men [30].

THE AIM

Purpose of research – improve diagnosis for abdominal forms of cryptorchism at the children through implementation innovative methods in practice (laparoscopic diagnostics).

MATERIALS AND METHODS

For a period from 2014 to 2017 years in the surgical department of Municipal Establishment «Dnipro specialized clinical center of mother and child named by professor M.

F. Rudnev» of Dnipro Regional Council» were carried out 43 diagnostic laparoscopy in a case of non palpated testicle syndrome. By age children were distributed into the following groups: up to 1 year -18 children, 1-2 years – 25 children.

All children with diagnostic purpose were performed laparoscopy, according to standard procedures under the total intravenous anesthesia with artificial ventilation of lungs and endotracheal method (recofol at the dose 8-10 mg/kg/hour). Intervention was performed in a position of patient on the back. The first 5 – mm obtuse troacar was input

into abdominal cavity and was carried out pneumoperitoneum (8-10 millimeters of mercury). After that we performed inspection of abdominal cavity, using laparoscope (5 mm, 30º). If necessary (in 20% of cases) to the left side of abdominal cavity was injected additional 3–5 mm troacar for the probe – palpator.

For comfort inspection of abdominal cavity patient was placed in the Trendelenburg position with inclination to one or another side up to 30º. At the diagnostic laparoscopy was assessed the following indicators: condition of internal inguinal ring and vaginal sprouts of a peritoneum (presence or absence, its obliteration), presence, location and size of a testicle, degree of an epididymis development and its correlation with the testis, presence, level of development, location of the testicular vessels and ductus deferens.

RESULTS

In children with abdominal location of testicles at the diagnostic laparoscopy were evaluated the following parameters: location, size of the testicles, condition of epididymis, testicular vessels and ductus deferens. Size of testicles, which were located in the abdominal cavity, was divided in the following stages: length – 7.0 ±2.0 mm, width 5.0 ± 1.0 mm (n=41). In all cases of abdominal cryptorchism testicles were located in the abdominal cavity near inguinal ring. There was shown hypoplasia of the testicles and epididymis, insufficient length of testicular vessels.

According to the results of diagnostic laparoscopy, we have chosen different tactics. Conservative therapy was shown at the absence indications for surgical intervention for a ptosis of testicle into scrotum (at the testicular agenesis). It takes place a blind termination of the testicular vessels and ductus deferens. Testicles were absent in general. The given case history was found at two boys 1 and 2 years old. After laparoscopic diagnosis and diagnosis of the testicle agenesis, for these children was recommended treatment by endocrinologist, because there were signs of hypogonadism and delayed of physical development.

Open revision of an inguinal canal was performed at the absence signs of abdominal placement of testis and absence endoscopic signs of a testicle agenesis. So, at the boy 2 of years old an inspection and palpation of inguinal area caused suspicion on the abdominal form of cryptorchism. There was recommended a diagnostic laparoscopy in order to clarify localization and state of the testis. As had been shown, in this case, the testicle was situated in the upper third of inguinal canal, was severe hypoplasia, having a numerous short testicular vessels. Therefor, we have to carry out an open inspection of the inguinal canal and performed surgical operation of testicle ptosis into a scrotum from laparotomic access.

Cases of laparoscopic picture of the testis rudiment at the presence of rudimentary gonads in the abdomen or in the initial part of inguinal canal we did not found. Two-stage orchiopexy at the different variants of testis location in the abdominal cavity was performed in 41 children. Bringing down of testis in these cases was carried out in some stages. In the first stage, during diagnostic laparoscopy, was performed treatment of a vascular bundle on a damaged testicle by Fowler – Stephens (operation a "long loop duct", which included crossing of testicular vessels with maximum spare of collaterals between testicle artery and arteries of the ductus deferens and muscle, which lifting the testicle). It was performed dissection of testicular vessels by Fowler – Stephens with overlay a clip on the testicular artery and incision of the testis albuminous cover (wound should be bleeding 2–3 minutes). This operation was shown at the insufficient length of the testicular vessels and inability to perform other simultaneous orchiofixing. The second stage was performed after 6–8 months after laparotomy. Fixation of the testicles into the scrotum was carried out by Petrivalsky (fixation in the testicle in an albuminous cover till a bottom of the scrotum was performed directly under a skin from the side of surgerical intervention). One should consider this method of fixing of the testicles in a scrotum as well as the simplest, most reliable and preferred by majority of authors.

Thus, the diagnostic laparoscopy allowed in the majority of cases to determine location of the testicle, its condition and developed further treatment tactics.

DISCUSSION

Review of methods for the diagnosis of abdominal cryptorchism in children was carried out. The diagnosis of cryptorchism received a lot of attention in the world and national literature. There were used a variety of research methods. For example, with using of orhivolumetry and testimetry, one can determine the linear dimensions and volume of the gonad; a study of hormone levels, radioisotope studies help to assess the function of both testicle and endocrine system.

Pelviography has been proposed for the detection of abdominal gonad in the abdominal form of the disease. With the development of science, new methods of examining patients appeared. Immediately after its appearance, ultrasonography occupied a firm place among the methods of cryptorchism diagnostics, since it allowed determining the location, size and structure of the gonads with a sufficiently high accuracy. The use of the technique based on the doppler effect, which allows to investigate a blood flow in the testicular parenchyma. At the same time, the assessment is not only qualitative, but also quantitative, since it became possible to measure the blood flow parameters: blood flow velocity during systole, blood flow velocity during diastole, resistance index.

If ultrasound diagnostics of internal organs devoted many works described in the world literature, then the works that are devoted to the dopplerography of the gonads, especially in children, are rare. Meanwhile, this diagnostic method allows evaluating hemodynamic in the gonad at a qualitative and quantitative level, and indirectly judging the state of the testicular parenchyma. Diagnostic laparoscopy has become a method that has become an integral and indispensable part of the diagnosis of abdominal cryptorchism and determination of treatment tactics. This method is successfully used for the differential diagnosis of abdominal cryptorchism and testicular agenesis. Minimally invasiveness in combination with highly informative made this method the leading one in diagnosing these forms of pathology.

If for the diagnosis of inguinal localization of the testicle visualization of the inguinal and caudal area and its palpation (in some cases, there is a need for ultrasound examination) is enough, then for the verification of localization of the gonads at the syndrome of unpalped testicles there is a need for a number of diagnostic methods, in particular, ultrasonography, computer or magnetic resonance imaging and surgical revision of the inguinal canal. In 1976, N. Cortesi applied laparoscopy as a method for diagnosing presence and condition of the testicle with cryptorchism. From that time, it was possible to make a visual assessment localization of the testicle and its size, to establish the reason for not testifying and, depending on the obtained data, to select an adequate tactic for correction of the detected pathological condition. Depending on the size of the testes, one can judge about the presence or absence of hypoplasia, its location in the abdominal cavity. The development of low-invasive technologies also allowed applying classification of cryptorchism, which defines further therapeutic tactics.

For unpalpated testicle, laparoscopic diagnosis with two-stage lowering of the testes was proposed by Godbole P.P., Najmaldin A.S. Laparoscopy gives a credible positive diagnosis, which is especially valuable in testicular aplasia, polyorhidia, and other cases, where laparoscopy is only method of diagnosis and treatment.

The use of diagnostic abdominal forms of cryptorchism in children with laparoscopy allows not only to clarify localization of the testicle, but also to assess its condition, which affects the further treatment tactics. In the structure of cryptorchism, according to our data, diagnostic laparoscopy of abdominal form took place in 22 cases (95.7%), "high" inguinal form - in 1 child (4.3%). In 21 cases, the testes were hypoplastic (91.3%) and 2 patients (8.7%) were diagnosed aplasia of the testicle. A two-stage orhyopexia with processing of the vascular bundle of the cryptorchid testis by Fowler-Stephens was performed on 21 boys (91.3%). Atrophy of the lowered testicle in the postoperative period was not observed.

In diagnostic laparoscopy, we evaluated the following parameters: condition of the internal inguinal ring and vaginal process of the peritoneum (presence or absence of its obliteration), the presence, placement and size of the testes, degree of development an appendage and its relationship with the testicle, presence, developmental stage, location of testicular vessels and ductus deference. In the children with abdominal placement of the testicles in all cases was hypoplasia of the testicles, insufficient length of testicular vessels.

By the results of diagnostic laparoscopy, we chose a variety of tactics. At the same time, testicular vessels and ejaculatory ducts were blindly ended. This situation was observed in two boys of 6 and 7 years old, whose parents first turned to a children's hospital with complaints about absence of a testicle in the scrotum. After the laparoscopic diagnosis and diagnosis of aplasia of the testicle, these children were recommended for treatment at the endocrinologist.

Therefore, in our opinion, laparoscopy is one of the most effective methods of diagnosis in children with an abdominal form of cryptorchism, regardless of the child's age. Laparoscopy allows to determine the further tactics of surgical treatment of a child with abdominal form of cryptorchism: when the testicle is located below the external pleural vessels and available loop of the ejaculatory duct, one-stage ophidopexia is possible, and when the testicle is located above the external pleural vessels and if there is no loop of the ejaculatory duct, a two-stage operation by Fowler-Stephens is carried out. In the given article presents an approach to treatment only a small number of patients requiring orhopexy in a case of abdominal cryptorchism. The positive results lead us to the continuation a set of clinical material and further improvement of operational technology.

CONCLUSIONS

1. Laparoscopic diagnosis abdominal forms of cryptorchism is the most reliable method in a comparison with computed tomography, ultrasound, radioisotope studies.
2. Procedure of laparoscopic diagnosis could show not only location and condition of the testis, blood vessels and ductus deferens, but help to develop the further treatment tactics.
3. Diagnostic laparoscopy abdominal forms of cryptorchism in children should be recommended for a wide application in the clinical practice.

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GENERAL CARDIOVASCULAR RISK AND FUNCTIONAL INDICATORS OF THE PERMANENT ATRIAL FIBRILLATION

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ABSTRACT

Introduction: No doubt today that atrial fibrillation (AF) is associated with an increased risk of thromboembolic events. Simultaneously we did not find any investigation about the links between general cardiovascular risk (GCVR) and the frequency forms and functional parameters of the heart in patients with AF.

The aim: To study the frequency forms and functional indices of the heart in patients with permanent AF in GCVR groups.

Materials and methods: 157 patients with permanent AF (99 men and 58 women) aged 64.6 ± 9.7 years were examined. The frequency of ventricular contractions, the duration of the ventricular complex (QRS), the corrected QT interval (QTc), power indices of the spectrum of heart rate variability (HRV) were measured by ECG. Echocardiographic parameters were studied using a SIM 5000 plus medical diagnostic automated echocardiograph. Patients were classified into GCVR groups.

Results and conclusions: The existence of relationships of GCVR with frequency forms of AF and functional indicators of the heart was established. In patients of the class I-III GCVR groups, the tachysystolic form of AF prevailed. Its frequency increases with the rise of the GCVR class. In GCVR IV, redistribution of forms of AF occurs in the direction of normosystolic ones. Among the functional parameters of the heart, the left ventricular ejection fraction and the power of the HRV spectra are most closely associated with GCVR.

KEY WORDS: general cardiovascular risk, atrial fibrillation, functional indicators

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INTRODUCTION

The atrial fibrillation (AF) is one of the most common forms of arrhythmias in various populations, which is occur in most cases on the background of the cardiovascular diseases (CVD) [1, 2, 3]. For today, numerous studies have been conducted and the association of AF with an increased risk of stroke and other thromboembolic events has been proved. Based on it, the necessity of constant monitoring of cardiac hemodynamics, including heart rate and heart rate variability (HRV) in this cohort of patients, is substantiated [4, 5].

At the same time, we did not find any work on the study of the links between general cardiovascular risk (GCVR) and the frequency forms and functional parameters of the heart in patients with AF. Based on the literary data and our own experience, it can be assumed that the determination and analysis of these indicators will increase the objectivity of evaluating the effectiveness of treatment of patients with AF and their prognosis [6, 7].

THE AIM

The aim **is** to study the frequency forms and functional indices of the heart in patients with permanent AF in GCVR groups for developing and justifying of approaches to improve the effectiveness of its diagnosis and therapy.

MATERIALS AND METHODS

In the cardiology department of the Central Clinical Hospital of the Ukrainian Railways, Kharkov Research Institute of General and Emergency Surgery and Kharkiv outpatient clinics No. 6 and 24 (Ukraine), 157 patients with permanent AF (99 men and 58 women) aged 64.6 ± 9.7 years were examined. AF duration in these patients was from 3 months to 21 years. According to the inclusion criteria AF proceeded on the background of arterial hypertension (AH), coronary heart disease (CHD) and heart failure (HF).

Exclusion criteria from the study were stable effort angina of IV functional class (FC), acute coronary syndrome, valvular defects and heart failure of IV FC.

The following functional parameters were evaluated in patients. The frequency of ventricular contractions, the duration of the ventricular complex (QRS) and the corrected QT interval (QTc) were measured by ECG on a computer electrocardiograph "CardioLab 2000". The total power (TP) and the power of high (HF) and low (LF) frequencies of the HRV spectrum were evaluated in seven-minute intervals when recording a standard ECG. Echocardiographic (EchoCG) parameters, such as the left atrial dimension (LA), the left ventricular posterior wall thickness (LVPW), left ventricular end-diastolic diameter (LVEDD) and the left ventricular ejection fraction (LVEF), were studied using "SIM 5000 plus" medical diagnostic automated echocardiograph (Italia) according to the criteria of the European Association of Cardiovascular Imaging [8].

GCVR was calculated according to the SCORE scale [9]. Patients were classified to 4 GCVR groups: I – low, II – moderate, III – high and IV – very high risk.

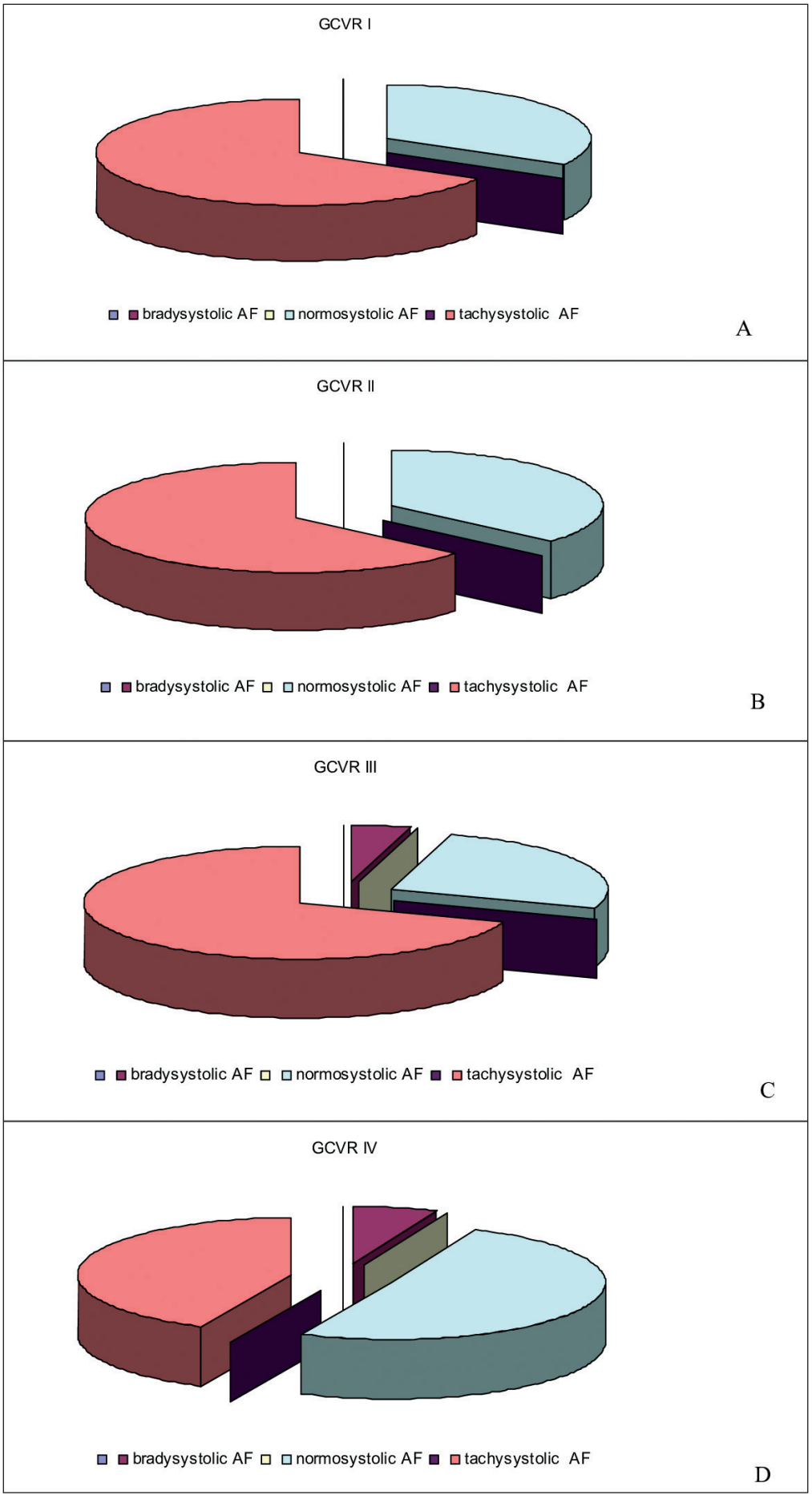

Fig. 1. Percentage of AF forms frequency in the GCVR groups

Table I. ECG indicators of atrial fibrillation in groups of general cardiovascular risk ($\overline{x} \pm s$)

Frequency forms of AF		GCVR			
		I – low n – 3	II – moderate n – 22	III – high n – 23	IV – very high n – 109
Normo-systolic	QRS, msec	92 ± 4,7	80 ±16,0	82 ±13,4	106** ± 7,3
	QTc, msec	430 ± 14,5	412 ±43,5	394 ±44,4	425 ± 27,2
Tachy-systolic	QRS, msec	87* ± 4,2	80 ±7,4	81 ±10,0	75* ±6,1
	QTc, msec	440 ±13,4	437 ±19,9	402 ±30,9	404 ±26,4

* p < 0,05 – within the GCVR group
** p < 0,05 – between GCVR groups

Table II. Echocardiographic parameters of patients with atrial fibrillation in groups of general cardiovascular risk ($\overline{x} \pm s$)

EchoCG parameters	GCVR			
	I – low n – 3	II – moderate n – 22	III – high n – 23	IV – very high n – 109
LA, mm	40 ± 5,2	39 ± 9,8	43 ± 4,3	39 ± 7,6
LVEDD, mm	47 ± 15,5	54 ± 7,3	58 ± 13,7	52 ± 7,5
LVEF, %	62* ± 1,9	54 ± 7,5	32 ± 15,4	57 ± 13,1
LVPW, mm	12,3 ± 0,3	11,4 ± 1,1	10,3 ± 2,3	13,9 ± 2,7

* p < 0,05 – between GCVR groups

Table III. HRV indices of patients with atrial fibrillation in groups of general cardiovascular risk (Me [Min – Max])

HRV	GCVR			
	I – low n – 3	II – moderate n – 22	III – high n – 23	IV – very high n – 109
TP, msec^2	13130 [10291-14509]	9597 [3931-57396]	7956 [5036-24918]	14577* [117-93417]
LF, msec^2	3656 [2586-4683]	2119 [967-17118]	1974 [1464-6382]	3701* [1313-30497]
HF, msec^2	8143 [6393-8207]	5480 [2555-30300]	5361 [2954-13659]	6157 [1839-31787]
LF/ HF	0,5 [0,4-0,6]	0,5 [0,3-1,1]	0,4 [0,4-0,9]	0,5 [0,3-1,2]

* p < 0,05 – between GCVR groups

In a statistical analysis of the data, the verification of the distribution of quantitative characters in accordance with Gauss's Law was conducted taking into account the asymmetry and excess. The formation of the databases was performed in Excel program. The obtained results were analyzed by the methods of parametric and nonparametric statistics with the determination of the minimum (Min), maximum (Max), median (Me) and with the calculation of the mean ($\bar{x}$), standard deviation (s). The determination of statistically significant differences between the groups was carried out using the Student's (t) and Kruskal-Wallis criteria (H).

RESULTS

In the groups of patients with risk I, II and III GCVR the tachysystolic form of AF dominated with a tendency to increase its percentage contribution with raising in the degree of GCVR (Fig. 1). Accordingly, the incidence of normosystolic AF in these groups decreased with an increase in the class of GCVR III. In patients with risk IV GCVR, there was a redistribution of the frequency of occurrence of AF forms in the direction of increasing the normosystolic AF frequency because of a decrease in the frequency of tachysystolic AF.

The frequency of occurrence of bradysystolic AF was low: from 0% in the groups of GCVR I and II to 4% in the group of GCVR III and 6% in the group of GCVR IV.

The mean values of QRS and QTc for tachysystolic and normosystolic AF did not significantly differ in the GCVR groups (Table I). Their values in bradysystolic AF were not evaluated due to its low occurrence.

EchoCG indicators in patients with permanent AF in the groups of GCVR are presented in table II. The size of the

LA, LVEDD and LVPW in the compared groups did not significantly differ. LVEF decreased from GCVR group I to group III with a slight increase in GCVR group IV.

Heart rate variability indices in patients with permanent AF in the GCVR groups are presented in Table III. Significantly lower values of HRV power were observed in GCVR groups I – III compared to the values ($p < 0.05$) in GCVR group IV.

DISCUSSION

As already noted, while the GCVR is an important criterion in assessing the health status and prognosis of patients with CVD [10, 11], it has not yet been evaluated depending on the presence of AF.

Our data show that with an increase in the degree of GCVR from I to III, the frequency of tachysystolic AF increases and normosystolic AF decreases. In grade IV GCVR with the expected further increase in the frequency of tachysystolic and a decrease in bradysystolic AF, a decrease in the frequency of the first one and an increase in the second one was unexpected. It can be explained, on the one hand, by more intensive drug therapy of patients of this group of GCVR and, on the other, by a possible earlier natural withdrawal of patients with tachysystolic AF [12, 13, 14].

The absence of statistically significant differences in the QRS and QTc values of the ECG between the groups of GCVR is due to the fact that they are not among the criteria for GCVR [9] and are not clinically significant for assessing the patient's condition and prognosis.

The decrease of LVEF observed with an increase in the class of GCVR confirms the significance of GCVR in the interpretation and assessment of the pumping function of the heart [15]. The powers of HRV spectra that are twice as high in GCVR group IV compared with GCVR groups I - III indicate significant changes in the rhythmic organization of the heart at degree IV GCVR, which, in addition to the above, explain the change in the ratios in the frequencies of tachy- and normosystolic AF in this group against other observed groups. The obtained results which indicated the progression of dysregulation of the heart rhythm in patients with grade IV GCVR should be regarded as prognostically unfavorable.

CONCLUSIONS

1. GCVR is important in the clinical evaluation of patients with persistent of AF establishing the existence of links with frequency forms of AF and functional indicators of the heart.
2. In patients with GCVR class I, II and III the tachysystolic form of AF dominates. Its frequency increases with the rise of the GCVR. At IV GCVR class there is a redistribution of the forms of AF to the direction of normosystolic one. The bradysisystolic form of AF is rare.
3. Among the functional parameters of the heart, the left ventricular ejection fraction and the power of the HRV spectra are most associated with GCVR.
4. It seems advisable to evaluate GCVR in patients with permanent AF for the analysis of the patients' condition and further prognosis of their condition.

It is promising to study of these functional indicators in patients with persistent AF.

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PATTERN OF ACTIVE BLOOD DONORS DONATING FOR MORE THAN 10 YEARS BASED ON THE RESULTS OF LABORATORY, MORPHOLOGIC, BIOCHEMICAL AND BIOPHYSICAL TESTS OF PERIPHERAL BLOOD

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ABSTRACT

Introduction: In spite of the lately increasing number of scientific research programs on donor blood storage, integrated solution of this problem remains a challenging open issue.
The aim: upon the study of laboratory, morphologic, biochemical and biophysical properties of donor blood erythrocytes, determine pathogenesis of abnormalities in erythrocytes of blood donors depending and increase effectiveness of early diagnostics and prevention of the above changes for donors' health protection.
Materials and methods: 215 blood donors (112 men and 103 women) were examined, among which 55 were active donors (29 men and 26 women) donating on regular basis, no less than 3 times a year and 160 first-time registered donors (83 men and 77 women). First-time registered donors made the control group of our research. The following methods were used: general blood tests, blood chemistry, radioimmune and enzyme-immunoassay, statistic methods.
Results: Results of the performed laboratory, morphologic, biochemical and biophysical tests: erythrocyte index determination, reticulocyte count, red blood cell distribution width, optical transmission of erythrocytes, test for aggregation and penetrability of erythrocyte membranes, effectiveness of erythropoiesis value determination in regular donor's and first-time donors erythrocytes demonstrated that the examined person making the group of donors are practically healthy people whose test results are within normal limits for their age group.
Conclusions: In order to preserve health of donors and ensure quality of blood components received at the time of donation, thorough checkup of donors, including, apart from the main and biochemical peripheral venous blood parameters, morphologic, biophysical and rheological parameters of erythrocytes is highly recommended before donation.

KEY WORDS: blood donors, erythrocytes, morphological changes, donation

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INTRODUCTION

Blood transfusion service and its social component – donor ship must be the priority areas of the state policy because the results of its work are of paramount importance. The main task of the blood transfusion service is supply of high quality components for blood transfusion therapy. Quality of blood components is compliance of properties and specifications of the blood component supplied to the recipient with the set standards. Strict order of conformance with the approved regulations and procedures is important at all technological states and is a cornerstone of blood transfusion service products quality. All actions, planned and implemented, starting with planning donor ship and ending with the finished product manufacturing and storage conditions, are important for ensuring the quality as the final result [1- 3].

In spite of the lately increasing number of scientific research programs on donor blood storage, integrated solution of this problem remains a challenging open issue [4-7].

THE AIM

The aim: upon the study of laboratory, morphologic, biochemical and biophysical properties of donor blood erythrocytes, determine pathogenesis of abnormalities in erythrocytes of blood donors depending and increase effectiveness of early diagnostics and prevention of the above changes for donors' health protection.

MATERIALS AND METHODS

215 blood donors (112 men and 103 women) were examined, among which 55 were active donors (29 men and 26 women) donating on regular basis, no less than 3 times a year and 160 first-time registered donors (83 men and 77 women). First-time registered donors made the control group of our research. The study included 160 first-time registered donors (83 men and 77 women) who donated in clinical centers of the Chair of Hematology and Transfusion Medicine of Shypyk National Medical Post-Graduate Academy of the Health Ministry of Ukraine. According to the age classification (WHO, 1991), first-time donors were divided into three subgroups: young donors – 48 (26 men and 22 women) aged 20-34, middle-aged donors – 62 (30 men and 32 women) aged 35-44, ripe age donors (27 men and 23 women) aged 45-59. All donors were examined pursuant to the Medical Examination Procedure for Donors of Blood and (or) its Components approved by Decree of the Health Ministry of Ukraine no. 385 dated 01.08.2005 – "On Infectious Safety o

Donor Blood and its Components" as donors whose blood is used for production of components.

Group of regular donors (RD) – 55 donors (29 men and 26 women) donating for more than years (number of donations in men was 48,95±1,38 (from 37 to 59), in women - 49,00±5,11 (from 39 to 66). Mean age of RD was 44,82±1,28 (32 – 56 years old). Mean age of male donors was 44,27±1,44 (32-54 years old). Mean age of female donors was 46,83±2,86 (40-56 years old).

Before donation, blood donors filled questionnaire and were examined by qualified specialists pursuant to the requirements of the applicable Medical Examination Procedure for Donors of Blood and (or) its Components. Hemoglobin was measured for all the donors (RR: M – no less than 130 g/l, F – no less than 120 g/l). Blood donation volume was determined on the basis of hemoglobin test (max volume – 450 ml excluding blood volume drawn for the test (up to 40 ml). For active blood donors, it is necessary to consider the interval before the donations that should not be less than 60 days from the date of the previous donation, as well as number of donations per year – no more than 5 for men and 4 for women. After blood donation, alanine aminotransferase (ALT, RR 0,1 – 0,68 mmol/h-l) level was measured in donors' blood; it was also tested for hemotransmissive infections (HIV ½, hepatitis B, hepatitis C, syphilis). Mean age of the first-time donors was 38,90±1,31 (20-59 years old). Mean age of the male donors was 39,66±1,53 (22-59 years old). Mean age of female donors was 37,56±2,45 (20-57 years old).

All 215 donors were practically healthy and eligible for donation subsequent to the result of survey, examination by specialists and hemoglobin level. Markers of transfusion transmissive infections were all negative. ALT level was within the normal limits. Research was approved by the Ethics Committee of Shupik National Medical Post-Graduate Academy of the Health Minstry of Ukraine.

Hemoglobin measuring, erythrocyte, leukocyte, platelet count and calculation of RBC indices were performed in the laboratory of the State Enterprise Road Blood Transfusion Station of the Northwestern Railway on the automated analyzer PCE-210 (ERMA, Japan). Determination of serum iron was performed according to batophenantroline method. Total iron binding capacity (TIBC) was evaluated by transferrin (TF) saturation with three-valence iron. Unsaturated (latent) iron binding capacity (UIBC) was calculated as difference between TIBC and iron concentration. TF saturation coefficient (TSC) was calculated as serum iron (SI)/TIBC ratio. Serum TF was determined by TIBC value. Serum ferritin (FN) was evaluated by radioimmunoassay technique using "IRMO-Ferritin" set (Belarus). Blood viscosity parameters, aggregation of erythrocytes and platelets were determined in accordance with S.I. Moiseev et al. (1990) method – panel of methods allowing for evaluation of the main parameters that are determinative for blood viscosity properties – aggregation of platelets and erythrocytes, erythrocyte deformability, hematocrit. Optical transmission of erythrocytes (OTE) was determined in accordance with D. Danop, I. Marikovaski (1964) method. Physical and chemical parameters of erythrocyte membrane penetrability (PEMP) was evaluated in accordance with O.I. Kulapina et al. (2006) method. Red blood cell distribution width (RDW) was determined automatically on automated hemo analyzer PCE-210 (ERMA, Japan). Effectiveness of erythropoiesis value (EEV) was evaluated in accordance with G.I. Kozinets et al. (1988) method.

All data obtained in the course of research were statistically processed. Research scope sample was analyzed by Student's t-test and Mann-Whitney nonparametric U-test, correlation and dispersion analyses. For data analysis, IBM SPSS Statistics 22.0 and Excel XP were used.

RESULTS AND DISCUSSION

In first-time donors, mean hemoglobin level was 138,88±0,95 g/l: in men - 142,72±0,81 g/l(135 g/l - 150 g/l), in women – 132,06±0,89 g/l (127 g/l - 140 g/l). Hemoglobin level was higher in male than in female donors ($p<0,001$). In first-time donors, erythrocyte count was, on an average, $4,63±0,03×10^{12}$/l. In the examined male donors it was, on an average, $4,76±0,03×10^{12}$/l ($4,5×10^{12}$/l - $5,0×10^{12}$/l), in female – $4,40±0,03×10^{12}$/l ($4,2×10^{12}$/l - $4,7×10^{12}$/l). Erythrocyte count was higher in men than in women ($p<0,001$). In the examined male donors, leukocyte count was in the mean $6,86±0,21×10^{9}$/l ($4,4×10^{9}$/l - $8,6×10^{9}$/l), in female – $6,79±0,29×10^{9}$/l ($8×10^{9}$/l - $9,2×10^{9}$/l). Average leukocyte count in the group of first-time donors was $6,83±0,17×10^{9}$/l. In first-time donors, platelet count was, on an average, $203,40±1,97×10^{9}$/l. In the examined male donors it was, on an average, $204,38±2,69×10^{9}$/l ($180×10^{9}$/l - $230×10^{9}$/l), in female – $201,76±2,71×10^{9}$/l ($190×10^{9}$/l - $210×10^{12}$/l). Erythrocyte count was higher in men than in women ($p<0,001$). In the group of first-time donors, reticulocyte count was, on an average, 0,88±0,05 ‰. In the examined male donors, mean reticulocyte count was 0,87±0,05, in female – 0,88±0,04 ‰. There were no significant age- or sex-dependent differences between mean leukocyte, platelet and reticulocyte counts in the examined first-time donors ($p>0,05$).

Mean cell hemoglobin (MCH) was, on an average, 30,63±0,25 pg (27-33 pg). In female donors, mean MCH was 29,40±0,42pg (27-31 pg), in male - 31,13±0,24pg (28-33pg). There was no significant sex-dependent difference in MCH in the examined first-time donors ($p>0,05$). Mean corpuscular volume (MCV) was, on an average, 93,41±0,91 (84-97 fl). In female donors, mean MCV was 94,22±1,69fl (89-97 fl), in male – 92,29±1,01fl (84-96 fl). There was no significant sex-dependent difference in MCV in the control group ($p>0,05$).

In all first-time donors, mean corpuscular hemoglobin concentration (MCHC) was, on an average, (34,38±0,23% (33-35%). In female donors, mean MCHC was 34,35±0,31% (33-35%), in male – 34,41±0,41% (33-35%). There was no significant age- or sex-dependent difference in MCHC in this group ($p>0,05$).

We performed cytometry of peripheral blood erythrocytes of the first-time donors. Mean corpuscular diameter was, on an average, 7,192±0,06 mcm^3, micro- and schistocytes - 4,80±0,14fl, anisocytosis - 4,02±0,14%, discocytes - 80,41±0,45%, abnormal shape - 19,59±0,55%. There was no significant age- and sex-related difference between average mean corpuscular diameter, micro- and schistocyte count, % of anisocytosis, discocytes and abnormally shaped erythrocytes in first-time donors ($p>0,05$).

In first-time donors, mean serum iron (SI) was 20,04±2,03 μmol/l, and it was higher in male donors ($p<0,01$), TIBS was, on an average, 57,25±2,49 μmol/l. In the examined male donors, TIBS was, on an average, 56,52±2,37 μmol/l (52,05 - 61,03 μmol/l),

in female – 58,55±2,20 μmol/l (54,87 - 62,05 μmol/l). TIBS was higher in females (p<0,01).

In the examined male donors, UIBS was, on an average, 35,77±4,07 μmol/l (28,05 - 43,37 μmol/l), in female - 39,78±3,53 μmol/l (34,18 - 45,65 μmol/l). In general, the mean UIBC for the group of the first-time donors was 37,21±4,31 μmol/l. UIBC was higher in females (p<0,01).

TSC was, on an average, 35,18±4,90 %. In the examined male donors, man TSC was 36,88±4,74 % (28,60 - 46,10 %), in female – 32,17±3,63 % (26,40 - 38,30 %). TSC was higher in male donors (p<0,01).

Serum TF was, on an average, 2,23±0,10 g/l. In the examined male donors, serum TF was 2,20±0,09 g/l (2,03 - 2,38 g/l), in female – 2,28±0,09 g/l (2,14 - 2,42 g/l). Serum TF was higher in female donors (p<0,01). In the examined male donors, serum FN was, on an average, 24,91±2,14 mcg/l (20,64 - 30,12 mcg/l)in female – 19,19±1,41 mcg/l(17,15 - 21,82 mcg/l). In general, the mean serum FN in the group of first-time donors was 22,85±3,36 mcg/l. Serum FN was higher in male donors (p<0,001). In young donors, serum iron was, on an average, 21,43±1,56 μmol/l (19,1 - 24,0 μmol/l), in middle-aged donors - 20,17±1,86 μmol/l (17,4 - 24,6 μmol/l), in ripe age donors - 18,03±1,14 μmol/l (16,4 - 19,8 μmol/l). Serum iron level in young first-time donors was higher than in middle-aged (p<0,05) and ripe age (p<0,001) donors. The level of serum iron in middle-aged donors was higher than in the ripe age donors (p<0,01). Average level of serum TF in young donors was 2,13±0,06 g/l (2,03 - 2,24 g/l) in middle-aged - 24±0,05 g/l (2,15 - 2,35 g/l), in ripe age - 2,35±0,05 g/l(2,26 - 2,42 g/l). Average level of serum FN in young donors was 24,01±4,17 mcg/ml (17,21 - 30,12 mcg/ml), in middle-aged donors - 22,88±3,08 mcg/ml (17,49 - 26,55 mcg/ml), in ripe age donors - 21,34±2,18 mcg/ml (17,15 - 24,21 mcg/ml). Serum FN in young donors was higher than in the ripe age (p<0,05). There was no significant difference in serum FN level between first-time young and middle-aged donors and middle-aged and ripe age donors.

In all first-time donors, RDW was 79,81±0,81 fl (79,01 - 80,71 fl). There was no significant sex-related difference in RDW in the examined first-time donors (p>0,05). The margin of errors for mean values for erythrocyte populations varied between 0,4 – 4,1% of the reference value. In most cases, it did not exceed 1-2%. According to the criteria approved for biology and medicine, accuracy achieved in the process of research is quite high. The data obtained is reliable and can be used both in practical work and as reference points. In first-time donors, OTE was 0,006±0,001 g/ml (0,005±0,001 - 0,007±0,001 g/ml). There was no significant sex-related difference in OTE in the examined first-time donors (p>0,05). There was no significant sex-related difference in erythrocyte aggregation, platelet aggregation index and hematocrit in first-time donors (p>0,05).

We established that in the group of first-time donors solid concentration in erythrocytes (%) was 43,74±0,11 g per 100 ml, solid content in erythrocyte was 27,54±0,17 pg, water content in erythrocyte - 67,09±0,18 %, PEMP - 1,49±0,01 U. There was no significant sex-related difference in solid concentration in erythrocyte, solid content in erythrocyte, water content in erythrocyte and PEMP in first-time donors (p>0,05).

We established that in the group of first-time donors erythrocyte fragmentation was, on an average, 1,74±0,09 % (0,75 - 3 %). There was no significant sex-related difference in erythrocyte fragmentation in first-time donors (p>0,05).

We established that in the group of first-time donors EEV was 0,070±0,001·10^{12}/l: in female donors it was, on an average, 0,069±0,0021·10^{12}/l, in male donors - 0,071±0,0019·10^{12}/l. First of all, EEV of 0,07±0,001·10^{12}/l in first-time donors demonstrates that this is the number of erythrocytes formed and is released daily into one liter of peripheral blood in this category of donors (hence in healthy people).

In RD, the results of the peripheral blood test were within the normal limits. It was established that mean hemoglobin concentration as well as erythrocyte, and platelet count was higher in male donors (p<0,05), while average leucocyte count was the same in both sexes (p>0,05). There was no significant difference in the mean parameters of peripheral blood between RD and control group donors (p>0,05).

We performed cytometry of peripheral blood erythrocytes in this group of donors. Mean corpuscular diameter was, on an average, 6,31±0,03 mcm^3, micro- and schistocytes - 6,21±0,23 fl, anisocytosis - 6,762±0,13 %, discocytes - 65,11±0,08 %, abnormal shape - 34,79±0,11 %. In the examined group RD, we detected significant reduction of the mean corpuscular diameter, discocyte percentage as well as increase of micro – and schistocytes, anocytosis and the number of abnormally shaped erythrocytes in comparison with the control group (p<0,05). These changes are suggestive of latent iron deficiency (LID) development.

In group RD, SI was 20,04±2,03 μmol/l. In the examined male donors, SI was 20,75±1,94 μmol/l (17,30 - 24,60 μmol/l), in women - 18,77±1,53 μmol/l (16,40 - 21,30 μmol/l). SI was higher in male donors (p<0,01).

In group RD, TIBS was, on an average, 57,25±2,49 μmol/l. In the examined male donors, TIBS was, on an average, 56,52±2,37 μmol/l (52,05 - 61,03 μmol/l), in female – 58,55±2,20 μmol/l (54,87 - 62,05 μmol/l). TIBS was higher in females (p<0,01). In the examined male donors, mean UIBS was 35,77±4,07 μmol/l (28,05 - 43,37 μmol/l), in female donors – 39,78±3,53 μmol/l (34,18 - 45,65 μmol/l). Average UIBS in group RD was 37,21±4,31μmol/l. UIBC was higher in females (p<0,01).

In group RD, TSC was, on an average, 35,18±4,90 %. In the examined male donors, man TSC was 36,88±4,74 % (28,60 - 46,10 %), in female – 32,17±3,63 % (26,40 - 38,30 %). TSC was higher in male donors (p<0,01). Serum TF was, on an average, 2,23±0,10 g/l. In the examined male donors, serum TF was 2,20±0,09 g/l (2,03 - 2,38 g/l), in female – 2,28±0,09 g/l (2,14 - 2,42 g/l). Serum TF was higher in female donors (p<0,01). In the examined male donors, serum FN was, on an average, 24,91±2,14 mcg/l (20,64 - 30,12 mcg/l), in female – 19,19±1,41 mcg/l(17,15 - 21,82 mcg/l). In general, the mean serum FN in group RD was 22,85±3,36 mcg/l. Serum FN was higher in male donors (p<0,001).

In all group RD, RDW was 70,28±1,93 fl (69,01 - 73,71 fl). There was no significant sex-related difference in RDW between the examined group RD (p>0,05), while there was significant difference in comparison with the control group (p<0,05). It was established that in group RD EEV was, on an average, 0,070±0,0010·10^{12}/l; in active female donors mean EEV was 0,069±0,0021·10^{12}/l, and in male donors it was respectively 0,071±0,0019·10^{12}/l, while there was significant difference in comparison with the control group (p<0,05).

Results of the performed laboratory, morphologic, biochemical and biophysical tests: erythrocyte index determination, reticulocyte count, RDW, OTE, test for aggregation and penetrability of erythrocyte membranes, effectiveness of erythropoiesis value determination in first-time donors erythrocytes demonstrated that the examined person making the control group of donors are practically healthy people whose test results are within normal limits for their age group.

In order to preserve health of donors and ensure quality of blood components received at the time of donation, thorough checkup of donors, including, apart from the main and biochemical peripheral venous blood parameters, morphologic, biophysical and rheological parameters of erythrocytes is highly recommended before donation.

It is recommended to add OTE to the list of screening tests for eligibility confirmation for active donors. In combination with affordability, time rate and simplicity, information value of this test will allow for its wide application in blood transfusion service institutions as a part of the eligibility screening.

CONCLUSIONS

1. It has been established that donation career of over 10 years leads to development of abnormalities of the main cytometric parameters of peripheral venous blood (we detected significant reduction of the mean corpuscular diameter of erythrocytes, discocyte percentage and increase of micro – and schistocytes, anocytosis and the number of abnormally shaped erythrocytes in comparison with the control group ($p<0,05$) and differences in biochemical parameters characterizing iron metabolism – mean SI, TSC, FN and FE were significantly different ($p<0,05$).
2. In the group of RD for over 10 years, we detected significant increase in the number of transformed erythrocytes (stomatocytes, echinocytes etc.) - 24,79±0,11 % vs.19,07±0,52 % in the first-time donors and, consequently, decrease in the number of normal discocytes - 72,11±0,08 % vs. 80,91±0,47 % in first-time donors, significant decrease of the corpuscular diameter of erythrocytes - 6,31±0,03 mcm^3vs. 7,22±0,04 mcm^3 in first-time donors, increased number of microcytes6,21±0,23 fl vs. 4,81±0,11flin first-time donors, and higher anisocytosis - 6,76±0,13 % vs. 4,01±0,12 % ($p<0,05$).
3. Morphometric assay, cytometry, OTE and RDW tests demonstrated that RD with donorship career of over 10 years had abnormalities of biophysical properties of erythrocytes. The following parameters were elevated in comparison with the control group (<0,05): PEMP - 1,57±0,01 U, erythrocyte aggregation - 17,01±0,03 %, OTE - 0,008±0,003 g/ml, RDW - 70,28±1,93 fl. These changes are secondary with LID.
4. It has been proven that longer donorship career leads to rheologic abnormalities in the peripheral blood and affects erythrocyte aggregation, deformability, hematocrit and OTE ($p<0,05$). RD had increased number of light fractions of erythrocytes and reduced number of heavy fractions ($p<0,05$). In the group of RD, correlation quotient between mean erythrocyte density and MCHC changes was $r=0,81$ ($p<0,001$).

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THE PHYSICAL DEVELOPMENT AND FUNCTIONAL STATE AS THE IMPORTANT COMPONENTS OF THE STUDENTS' HEALTH

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ABSTRACT

Introduction: The level of health and physical fitness of the students of Ukrainian higher educational institutions has worsened in recent years. It conditions the search for effective solutions to this problem and determines the significance of the investigation.

The aim: To investigate the level of physical development and functional state of the students of agricultural educational institutions during study.

Materials and methods: The investigation was conducted in Zhytomyr National Agroecological University in 2016–2018. Seventy three students (38 male and 35 female students) took part in the investigation. The level of physical development and functional state of students was defined according to the next tests: body length, body weight, wrist dynamometry, lung capacity, heart rate, systolic and diastolic blood pressure. The level of students' physical health was examined according to the methodology by G. L. Apanasenko and determined the interrelation of the levels of physical health of the students of different genders during the investigation.

Results: It is determined that the majority of the students' investigated indicators are not improved during the first and the second years of study ($p>0.05$). The level of the students' physical health remained unchanged during study. Moreover, the health level of both male and female students is rated as low during all stages of the investigation.

Conclusions: The conducted analysis proves the necessity of the current physical education system improvement at Ukrainian higher educational institutions in order to improve the students' physical development and functional state, health and efficiency of the educational and future professional activity.

KEY WORDS: physical education, physical development, functional state, health, students

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INTRODUCTION

The works of many scientists [1, 2, 3] mention that the level of physical development, health and physical fitness of the students of Ukrainian higher educational institutions has worsened significantly in the recent years and the majority of them have health problems. Therefore, the works of A. V. Mahlovany, V. S. Muntian and other authors [4, 5, 6] mention that the physiological age of the 20–24-years-old students exceeds the real one by 10–15 years. The investigations of G. L. Apanasenko [7] determine that the percentage of the male population who are in the safe zone of health level was decreased from 8 to 1 % in the last 20 years in Ukraine. The works of S. M. Futornyi, G. M. Budagiants and other scientists [3, 8, 9] mention that the number of students who have low and below the middle levels of somatic health was increased from 59 % in 2007 to 83 % in 2014.

E. G. Bulich, I. V. Muravov, M. S. Goncharenko, V. Y. Novykova and other scientists [1, 2, 5, 10] consider that the low level of health and physical fitness of students is conditioned by the low level of physical development and health of school graduates; lack of the students' interest, motives and need of traditional classes in physical education; insufficient health-promoting and training orientation of the means of physical education; studying conditions in the modern higher educational institutions that are characterized by increased studying capacity, low level of students' activity and their lifestyle.

The scientists [3, 10] consider that the students' physical activity should be increased during studying in order to improve the level of their physical fitness, development and health. Physical education is an indivisible component of the formation of developed harmoniously modern specialist [4, 11, 12]. The systematic physical activity is proved to

Table 1. The dynamics of the students' physical development and functional state indicators during the first and the second years of study at an agricultural higher educational institution (n=73, X±m)

The indicators examined	Terms of study				Significance value
	1st	2nd	3rd	4th	
Male students (n=38)					
Body length, sm	176.2±1.43	176.5±1.45	176.9±1.46	177.1±1.42	p>0.05
Body weight, kg	71.9±1.38	72.3±1.39	72.8±1.42	73.4±1.44	p>0.05
Handgrip test, kg	38.9±0.73	39.4±0.69	40.3±0.67	40.7±0.65	p>0.05
Lung capacity, ml	4073.1±91.6	4096.5±90.4	4107.8±89.8	4113.2±90.1	p>0.05
Heart rate at rest, beats/min	73.1±0.64	72.9±0.61	73.0±0.67	73.2±0.68	p>0.05
Systolic blood pressure, mmHg	121.1±0.93	121.6±0.91	121.5±0.95	121.7±0.98	p>0.05
Diastolic blood pressure, mmHg	74.6±0.89	75.9±0.88	74.2±0.85	74.9±0.83	p>0.05
Female students (n=35)					
Body length, sm	162.1±1.39	162.2±1.37	162.4±1.37	162.9±1.38	p>0.05
Body weight, kg	57.1±1.31	58.2±1.29	59.1±1.34	59.8±1.30	p>0.05
Handgrip test, kg	21.9±0.62	22.5±0.57	23.1±0.54	22.8±0.52	p>0.05
Lung capacity, ml	2827.2±84.3	2855.6±82.7	2881.5±83.1	2914.6±83.9	p>0.05
Heart rate at rest, beats/min	69.7±0.75	70.2±0.72	69.9±0.70	70.3±0.71	p>0.05
Systolic blood pressure, mmHg	116.2±1.05	116.5±1.02	116.6±0.99	116.4±0.98	p>0.05
Diastolic blood pressure, mmHg	70.9±0.76	71.1±0.72	71.0±0.74	71.2±0.71	p>0.05

promote the improvement of health, physical and mental capacity and quality of students' studying and health [1, 8, 13, 14, 15].

THE AIM

The aim of the article is to investigate the level of physical development and functional state of the students of agricultural educational institutions during study.

MATERIALS AND METHODS

The investigation of the students' indicators of physical development and functional state was conducted in Zhytomyr National Agroecological University in 2016–2018 (during the 1st – 4th terms). Seventy three students of the faculty of technology (38 male and 35 female students) took part in the investigation. The level of physical development and functional state of students was defined according to the next tests: body length, body weight, handgrip test (wrist dynamometry), lung capacity, heart rate, systolic and diastolic blood pressure. The level of students' physical health was also examined according to the methodology of the rapid qualitative assessment of the somatic health level (by professor G. L. Apanasenko [7]) based on the anthropometry indicators and the state of the cardiovascular system. The health level was evaluated in points and it included the estimation of the body mass index (the ratio of body weight to body length), life index (the ratio of lung capacity to body weight), Robinson's index (a product of heart rate and systolic blood pressure), power index (the ratio of the wrist dynamometry to body weight) and heart rate recovery after a standard exercise (20 squats in 30 sec). Besides, the interrelation of the physical health levels of the students of different genders was defined during the investigation.

The authenticity of the difference between the indicators of students at the beginning and at the end of the investigation was determined by Student's t-test and the dynamics of the indicators during studying was examined.

The methods of investigation: theoretical analysis and generalization of the scientific and methodological literature, pedagogic observation, medical and biological methods and methods of mathematical statistics.

RESULTS

The analysis of the body length showed that the indicators of both male and female students tend to insignificant increase during the first and the second years of study at an agricultural higher educational institution, but they remain approximately unchanged – the difference in body length indicators of men is 0.9 sm, women – 0.8 sm in the 1st and the 4th terms and it is not authentic (p>0.05) (Table 1). Body weight is a vital indicator of the physical development of students. The level and dynamics of body weight point to the conclusion on the efficiency of the physical education system at a higher educational institution. The examination of the body weight indicators proves that both male and female students have body weight gain during studying. Therefore, the body weight of male students was 71.9 kg in the 1st term and 73.4 kg in the 4th term, the difference is 1.5 kg (p>0.05). The difference in the average body weight of female students in the 1st (57.1 kg) and the 4th (59.8 kg) terms is 2.7 kg, but it is not authentic (p>0.05). The conducted

Table 2. The dynamics of the students' physical health level during the first and the second years of study at an agricultural higher educational institution (n=73, X±m, points)

Groups of students	Terms of study				Significance value
	1st	2nd	3rd	4th	
Male students (n=38)	2.31±0.54	2.48±0.59	2.61±0.60	2.73±0.62	p>0.05
Female students (n=35)	3.08±0.62	3.14±0.60	3.22±0.58	3.27±0.55	p>0.05

analysis of the students` body weight proved the lack of the efficiency of the current system of physical education at a higher educational institution in the improvement of the students' physical development. The body weight indicators of both male and female students are within the age norm during studying at an agricultural higher educational institution. However, considering a downtrend of the students' body weight increase during the first and the second years of study and the lack of classes in physical education in the last years of study, the students' body weight increase in the last years of study should be stated.

The analysis of the indicators of the more powerful arm handgrip test showed that both male and female students have the equal results in the 1st and the 4th terms authentically (p>0.05). The examination of the dynamics of arm muscles strength indicators proves their inauthentic increase by 1.9 kg for men and 0,9 kg for women during studying (p>0.05). The highest results in handgrip test of male students are recorded in the 4th term (40.7 kg), of female students – In the 3rd term (22.8 kg) (Table 1).

The investigation of the level and dynamics of the students' institutions of lung capacity proves that the indicators of the functional abilities of the respiratory system of both male and female students remained approximately unchanged during studying (Table 1). Therefore, the lung capacity indicators of male students were just 40.1 ml increased (p>0.05) during the 1st and the 2nd years of study and the indicators of female students were 87.4 ml increased (p>0.05) that means insufficient influence of the classes in physical education according to the current system on the improvement of the students respiratory system. The indicators of the lung capacity of both male and female students are within the age norm.

The results of the many scientists' researches [3, 10, 13] prove that physical exercises contribute to the improvement of the cardiovascular system activity indicators: the indicators of heart rate, blood pressure are decreased and recovery processes after exercises are hastened etc. However, the analysis of the heart rate at rest showed that the indicators of the students of both groups remained unchanged authentically during studying (p>0.05). The heart rate changes of the students have negative dynamics – the difference of the heart rate indicators in the 1st and the 4th terms of the male students is 0.1 beats per min and the female students – 0.6 beats per min (Table 1).

The analysis of the systolic and diastolic blood pressure indicators showed that although both male and female students have the downtrend of indicators in the first and the second years of study, the difference in the average results of the 1st and the 4th terms is not authentic (p>0.05) (Table 1). Therefore, the systolic blood pressure indicators of the male students were 0.6 mmHg worsened and of the male students – 0.2 mmHg worsened; the diastolic blood pressure indicators of both male and female students were 0.3 mmHg worsened. Additionally, the indicators of blood pressure are within the age norm.

Therefore, the analysis of the physical development and functional state indicators of the students showed that the majority of the characteristics investigated are not improved during the first and the second years of study at an agricultural higher educational institution (p>0.05). Additionally, such important indicators as body weight, heart rate have the downtrend that emphasizes the lack of efficiency of the current system of physical education.

The analysis of the students' physical health level showed that the dynamics of the total points according to the methodology by G. L. Apanasenko have a positive character during the first and the second years of study, but the indicators of the 1st and the 4th terms of both male and female students do not differ authentically (p>0.05) (Table 2).

Therefore, the total point of the male students' group was 2.31 points in the 1st term and 2.73 points in the 4th term; the difference is 0.42 points and it is not authentic (p>0.05). The total point of the female students' group was 3.08 points in the 1st term and 3.27 points in the 4th term; the difference is 0.19 points and it is not authentic (p>0.05). According to the methodology by G. L. Apanasenko, the health level of both male and female students remained unchanged during all stages of the investigation and it was estimated as low.

The qualitative analysis of the physical health levels showed that the absolute majority of the students (men and women) have the low and below the middle level of health during all stages of investigation. Therefore, the percentage of the students from the male group who have the low and below the low level of physical health is 81.6 % (47.4 % and 34.2 % respectively) in the 1st term, and 79 % (39.5 and 39.5 % respectively) in the 4th term (Fig. 1). The number of male students who have the middle level of physical health was increased from 13.2 % in the 1st term to 18.4 % in the 4th term. Additionally, the number of male students who have above the middle level of physical health was decreased by half (from 5.2 % in the 1st term to 2.6 % in the 4th term).

The dynamics of female students' physical health levels have a similar tendency. 54.3 % female students were determined to have the low level of physical health, 31.4 % – below the middle level, 11.4 % – the middle level and just 2.9 % – above the middle in the 1st term (Fig. 2). The percentage of female students who have a low level of physical health was

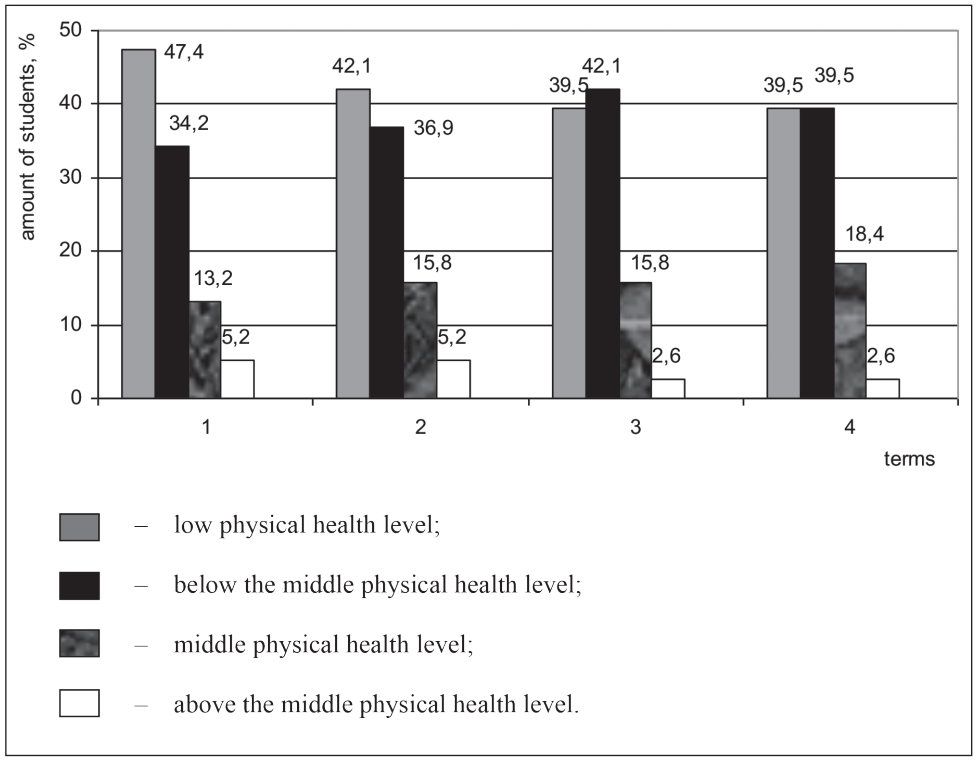

Fig. 1. The dynamics of physical health levels among male students of agrarian higher educational institutions during the first and the second years of study (n=38, %):
– low physical health level;
– below the middle physical health level;
– middle physical health level;
– above the middle physical health level.

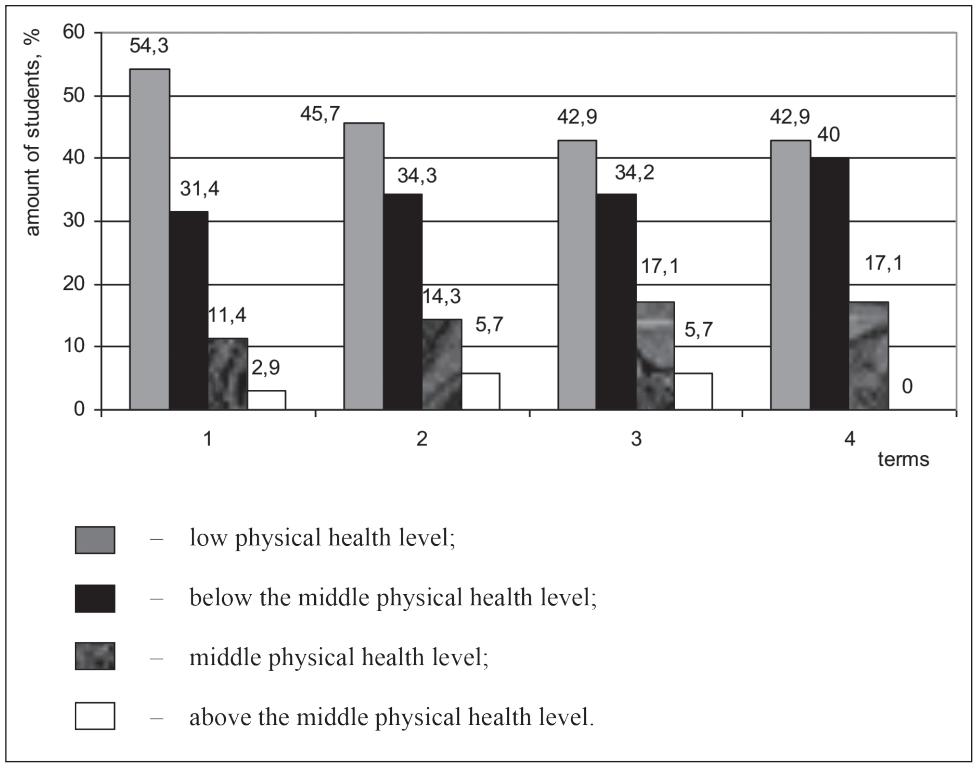

Fig. 2. The dynamics of physical health levels among female students of agrarian higher educational institutions during the first and the second years of study (n=35, %):
– low physical health level;
– below the middle physical health level;
– middle physical health level;
– above the middle physical health level.

decreased to 42.9 %, who have below the middle level was increased to 40 % and who have the middle level was 5.5 % increased (to 17.1 %) in the 4th term. It was determined no female students who have above the middle level of physical health in the 4th term that emphasizes the lack of the influence of the traditional classes in physical education on the physical health level of both male and female students.

It should be mentioned that neither male nor female students had a high level of physical health during study. Therefore, the analysis showed that the majority of students (more than 80 %) have low and below the low levels of physical health, more than 95 % students are out of the safe zone (12 points) according to the methodology by G. L. Apanasenko.

DISCUSSION

The World Health Organization defined approximate interrelation of different factors that ensure and form the health of a modern person, namely genetic factors (genetic heredity) – 20 %, environmental conditions (climate, ecological conditions) – 20 %, the level of health maintenance (health service support) – 8 %, life conditions and lifestyle (rational working, physical activity, nutrition, personal hygiene, discarding unhealthy habits) – 52 % [1, 5]. In particular, many scientists [2, 4, 6, 9] consider the conditions of life and lifestyle including various elements related to all aspects of health – physical, mental, social and psychic, to be the key factors of the students' health and working capacity improvement.

The works of many scientists [5, 10, 12, 14] mention that a great number of negative factors which cause health problems affect the students' organism systems during study. There are low physical activity, the amount of studying hours and days, emotional and mental stress, mental overloads especially during the exam terms, eating disorders (nutrition of a bad quality, poor nutrition, over nutrition and malnutrition), bad habits (smoking, abuse of alcohol, drug consumption etc) and others among them.

The world practice shows that physical activity plays an important role in health improvement and disease prevention [1, 3, 8, 13]. However, the situation concerning physical education and sport is critical in Ukraine. Only 13 % population is engaged in physical activity [3, 4, 11]. According to the data of many scientists [1, 2, 6, 10], the hard economic situation in post-soviet Ukraine had a negative impact on the development of physical education and popular sport at educational institutions. The number of students who belong to the physical education group with reduced exercise load and the special medical group is increasing and the number of healthy students is decreasing every year. The authors consider it to be conditioned by the lack of the traditional forms of physical education efficiency, modern students' lifestyle, low level of school graduates health. The scientists mention that the formation of a healthy lifestyle and engaging of the youth in the systematic physical activity should be one of the important areas of focus of higher educational institutions [2, 3, 6, 7, 13, 15].

The results of our research proved the conclusions of the works of many scientists on the insufficient level of physical development, functional abilities of the main organism systems and health of students. The investigation also shows the necessity of the improvement of the physical education system of students (men and women) in order to improve their physical state, health and efficiency of the studying and future professional activities.

CONCLUSIONS

The majority of the students' examined indicators of physical development and functional state are determined not to be improved during the first and the second years of study at an agricultural higher educational institution ($p>0.05$). Additionally, body weight and heart rate at rest have the downtrend that emphasizes the lack of efficiency of the current system of physical education. The level of the students' physical health remained unchanged during study according to the methodology by G. L. Apanasenko. Besides, the health level of both male and female students is evaluated as low. The analysis proves the necessity of the improvement of the system of physical education of the students at Ukrainian higher educational institutions in order to improve their physical state, health and efficiency of the studying and future professional activities.

The prospects of future investigations involve the research of the interrelation between the level of physical preparedness and the level of the students' physical health during study at higher educational institutions.

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ORIGINAL ARTICLE
PRACA ORYGINALNA

EFFECT OF PROBIOTICS ON ALTERED GUT MICROFLORA IN PATIENTS WITH SEVERE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

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ABSTRACT

The aim: To estimate intestinal microbial changes and study the efficacy of probiotic preparations in systemic inflammation.

Materials and methods: The study involved 202 patients with chronic infections various sites, including 58 (28.7 %) patients with respiratory tract infections, 56 (27.7 %) patients with infections of the genitourinary system, 48 (23.7%) - with purulent inflammatory postoperative complications, and 40 HIV-infected patients. We studied the quantitative and qualitative composition of intestinal microflora on the background correction of probiotic preparations.

Results: We have found quantitative and qualitative changes of intestinal microflora in all patients with chronic infections. Dysbiotic changes manifested in reducing the number of major orders symbionts (*Lactobacillus spp., Bifidobacterium spp, Escherichia coli* with normal enzymatic properties) and increase the number of pathogenic microorganisms (*Staphylococcus aureus, Clostridium spp., Candida spp.).* In all study groups after using probiotics, the number of pathogenic microorganisms *(S. aureus, S. saprophyticus, S. epidermidis, C. albicans, and Cl. perfringens)* were decreased and tended to restore normal range of microbial landscape.

Conclusion: So, dysbiotic disorders of the intestine in patients with chronic inflammation characterized by decrease in the number of basic gut symbionts and reducing its protective properties that accompanied the advent of pathogenic microorganisms. In our study probiotics demonstrated statistically significant improvements in the qualitative and quantitative composition of microflora.

KEY WORDS: microflora, dysbiosis, probiotics, systemic inflammation

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INTRODUCTION

Gastrointestinal (GI) tract is inhabited by more than 1,000 species of bacteria with total number of more than 10^{14} cells at a concentration of 10^7 to 10^{12} cells / g of intestinal contents.

Microbial community, developing together with the host during his lifetime, establishes with him, as a rule, a symbiotic relationship that favors their coexistence [1,2]. Intestinal homeostasis can be interpreted as a set of interactions between the host and microbiota colonizing the gut. This set includes motility, secretion, absorption, cellular composition, mitotic activity, the length of villi and crypts depth. It is generally recognized that the intestinal microflora plays an important role in human health and life [1,2]. Commensal flora has important and specific functions in metabolism, nutrition and protection from pathogens. The intestine is the largest immune organ of the human body. Protective bowel functions include three basic components: the intestinal flora, intestinal epithelium and the intestinal immune system. In recent years, it managed to more clearly define the role of microbiota in the formation and regulation of the immune system. Thus, the segmented filament bacteria activate Th17-cells [3], while *Clostridium* induce regulatory T-cells [4,5]. So, the intestinal microflora helps to preserve the delicate balance between the immunoregulatory (Treg) and proinflammatory (Th17) cells and can modulate the immune status of the adaptive immune response, which ensures the preservation of homeostasis. Invading pathogens can disrupt homeostasis, which leads to an intense immune response, accompanied by an inflammatory response and impaired intestinal barrier. Studies have shown a very low incidence of bacterial translocation, while maintaining a standard amount of obligate anaerobes in the intestine, from which it can be concluded that anaerobic bacteria are the main inhibitors of bacterial overgrowth and translocation of E. coli and other potentially pathogenic bacteria. Disorders of intestinal homeostasis, measured in a changing the qualitative and quantitative composition of the normal flora and, above all, reducing the number of anaerobic bacteria, impaired of the interaction between the microbiome and the host qualifies as dysbiosis, which can reduce the resistance of the intestine to pathogens. Thus, the intestinal flora may be a cause or a consequence of various pathological conditions of humans. In particular, the intestinal microbiota is considered as a possible etiological factor of several metabolic disorders and, at the same time, as an important therapeutic target in several pathological conditions [6].

In recent years, numerous evidence of the relationship of intestinal biocenosis with digestive tract diseases, cardiovascular system, obesity, diabetes, malignant neoplasms of the stomach, colon, breast cancer, allergic, autoimmune diseases, and others

has been received. [7,8]. Moreover, quite often cause of dysbiotic changes may be certain features of the diet. For example, it is proved that the rich in fats and carbohydrates "western diet", that is usable, ready meals, softens host protective responses that increase the survival of pathogenic and conditionally pathogenic bacteria and facilitates the colonization of mucosa [9,10].

The role of intestinal microbiota in the development of diseases has aroused interest to therapeutic use as probiotic agents. The use of probiotics has been very effective in treating various diseases. For example, probiotics containing bifidobacteria and lactobacilli have proven effectiveness in the treatment of respiratory infections, gastrointestinal diseases and diseases of urogenital system [11]. Probiotics, which include certain strains of lactic acid bacteria can not only reduce nasal colonization of pathogens (*Staphylococcus aureus, Streptococcus pneumoniae*, *beta-hemolytic Streptococcus*), but also to modulate the immune system in the diseases of the upper respiratory tract [12].

Except obligate anaerobes, an important place among the probiotic species occupies facultative anaerobic spore-forming bacteria *Bacillus subtilis* and *licheniformis*. These bacteria have a synergistic antagonistic effect of pathogenic organisms, while not inhibiting the resident. Probiotics based on them proved to be effective in the treatment of dysbacteriosis of different degrees of severity and origin, including dysbacteriosis of infants, yersiniosis, ulcerative colitis, acute intestinal infections in children [2] and others.

Probiotics are useful not only for treatment but also for prevention of various infections [13]. In general, probiotics proved to be quite effective and, most importantly, safe means of restoring lost as a result of the pathological process of intestinal homeostasis [14,15]. At the same time a number of outstanding issues remain. Therefore, in most cases, commercial preparations of probiotics were administered without regard to the quantitative and qualitative changes in the microbial landscape, although it is logical and justified to apply, especially those probiotics that are able to modulate and replace lost or impaired types of normality.

THE AIM

The purpose of this study was to analyze changes of the intestinal microbiota in systemic inflammation and the efficacy and safety of combination therapy, including the use of probiotics for the correction of dysbiotic disorders.

MATERIALS AND METHODS

PATIENTS

The study was conducted in an outpatient-health care unit of the Kharkiv Medical Academy of Postgraduate Education (KhMAPE). We examined 202 patients with chronic infections of different location, not amenable to standard therapy, which were divided into 4 groups:

I. (n=58) – Respiratory tract infections (obstructive bronchitis, bronchial asthma, glossitis, chronic tonsillitis, pneumonia). The dominant pathogen was *S.aureus*;

II. (n=56) – Infections of the genitourinary system (cystitis, pyelonephritis, prostatitis). The dominant pathogen was *E.faecalis*;

III. (n=48) – Pyoinflammatory postoperative complications. The dominant pathogen was *P.aeruginosa*.

IV. (n=40) – chronically HIV-infected adults. All the patients had been diagnosed according to the criteria of WHO with the III-IV stage of HIV infection. The dominant species was *E.coli*.

Inclusion criteria were the presence of clinical and laboratory signs of intestinal dysbiosis. Exclusion criteria included a data anamnesis of antibiotics and probiotics for the previous month. All patients were informed about the purpose and research plan and gave a written agreement to participate in the study.

The main symptoms and conditions attributed to intestinal dysbiosis include abdominal pain, bloating, flatulence, diarrhea, constipation, nausea and loss of appetite.

Laboratory analysis of stool has been investigated as marker of dysbiosis. The evaluation of dysbiosis may include comprehensive testing of various aspects of digestion, absorption, microbiology, and metabolic markers.

Microbial fecal analysis of the following components is considered investigational as a diagnostic test form the evaluation of intestinal dysbiosis:

- Levels of *Lactobacilli, bifidobacteria*, and *Escherichia coli a*nd other "potential pathogens," including *Bacillus cereus, Citrobacter, Klebsiella, Proteus*, *Pseudomonas, Salmonella, Shigella, Staphylococcus aureus, Vibrio;*

- Identification and quantitation of fecal yeast (including *Candida albicans, Candida tropicalis*).

FECAL BACTERIOLOGIC CULTURE

The study of qualitative and quantitative composition of microflora of the colon was carried out by plating ten-fold dilutions of faeces samples (10^1-10^9) on a standard set of selective and differential diagnostic medium for the selection of intestinal microorganisms [16].

The contents of the colon in an amount of 2-3 g was taken to the laboratory and processed within 2 hours in a sterile vial without preservative. Collection of material was carried out before the use of antibiotics and bacterial preparations (probiotics, prebiotics et al.).

Primary inoculation of clinical material was performed quantitative method on nutrient media in accordance with the regulations. Ten-fold serial dilutions of each fecal sample were performed and plated on selective and non-selective media for enumeration of the members of the intestinal microflora. Stool samples were placed on solid media (Bismuth Sulphite Agar, EMB Agar (Levine), Endo Agar, Blood Agar, Baird-Parker Agar, Sabouraud Dextrose Agar, Clostridial Agar, Rogosa SL Agar, Bifidobacterium Agar, HiMedia Lab., India). The plates were incubated at 37^0C for 24 or for 48 h. The incubated microorganizms were then counted and identified with accordance to standard procedures. Summarized data of control group (10 healthy adult's) microflora contents served as a normal standard.

During the survey, patients did not take medications with potentially possible effects on the gastrointestinal tract, including antibiotics.

Correction of dysbiotic disorders was carried out by taking into account the individual personified the intestinal flora changes. The structure included a cocktail commercial

preparations of probiotics complex ("Santegra", USA); Bifikol ("Biopharma Ukraine"); Laktiale ("Farmak", Ukraine). Due to the composition of preparations, probiotic complex was administered at reducing the number of *bifidobacteria* and *lactobacilli*, Bifikol - with a deficit of *E.coli*, Laktiale - with a decrease in the number of *bifidobacteria* and *lactobacilli* and *lactic streptococci*. The scheme of correction was calculated for 1 month of taking probiotics. Clinical and microbiological changes were evaluated before and after correction by probiotics.

All bacterial counts (colony-forming units (CFU)/g of wet feces) were transformed to logarithm (log_{10}CFU) for ease of statistical analysis.

STATISTICAL ANALYSIS

Statistical analysis was performed by using the statistical program «Statistika 10". Numerical data are presented as "mean value ± standard deviation». Statistical analysis of results were considered significant when p <0,05

RESULTS

Demographic characteristics of the study groups is shown in Table 1. Most of the patients showed signs of intestinal dysbiosis of various degree of severity. Dominated dyspeptic syndrome was also followed by pain and asthenovegetative syndrome.

Despite the clinical differences of presented forms of disease, all patients complained of recurrent pain in different parts of the abdomen, nausea, unstable stool, bloating of various severity. Thus, by the time of the study abdominal pain occurred in 70% of patients, disturbances of stool character presented in 91.9% of patients (diarrhea was predominant in 59.7%, stool retention - in 40.3%), nausea, lack of or reduced appetite in 58%, flatulence - in 85.8% of patients (Table 2).

Microbiological study revealed decrease in the concentration of *bifidobacteria* in fecal samples 3-4 orders of magnitude 5.0 ($<10^6$) in 77.6% of patients with diseases of the respiratory system, 92.9% - with diseases of urogenital system as well as in 93.8% - with postoperative complications. The number of *lactobacilli* in 80 - 83% of all patients groups also did not exceed 10^5-10^6 CFU/g. Assessing patients intestinal microbial landscape, it is noteworthy reduction in the amount of *E. coli* with normal enzymatic activity. Thus, in group I in 45 patients (82.7%), its concentration in 1 g of feces did not exceed 10^6 CFU / g, group II - 16 (29%), group III - 24 (50%). *E.coli* with hemolytic activity was not found.

It is worth noting a significant decrease in the concentration of the most important bacteria of the of the intestinal microflora - *Enterococcus*. Therefore, in all patients of group I and II the amount of *E. faecalis* and *E. faecium* in the colon was not in line with the reference values and became > 10^7 CFU/g, but in group III the concentration of enterococci was normal in 36 patients (75%). Fungi of the *Candida* were detected in stool samples in the amount of 10^4-10^6 CFU/g in 14% of patients in group I and 58% - in group III, at maximum permissible concentration of $\leq 10^4$ CFU/g.

HIV-induced dysbiosis appears to be characterized by decreased abundances of bacteria that are regarded as commensal or protective accompanied by an expansion of bacteria that are proinflammatory or pathogenic (Table 6). Thus, in 90% of cases the number of *bifidobacteria* was less than 5.9 ± 0.9 and in 10 % of cases it was about 7.0 ± 1.1. The number of very important *lactobacilli* at HIV infection is significantly reduced against healthy controls accounting less than 5.0 ± 0.8 in 87.5% and 6.7 ± 1.07 in 12.5% of patients against 7.7 ± 1.23 respectively ($p<0.05$).

Thus, changes in colon microflora were to reduce the number of indigenous microflora and its protective properties, which showed the emergence of pathogenic microflora of *S.aureus, S.epidermidis, S.saprophyticus, Cl.perfringens*, as well as *Candida* (table 3-6). Correction of dysbiotic violations within 1-2 weeks leads almost to the normalization of defecation and complete disappearance of other symptoms of intestinal dyspepsia such as flatulence and abdominal pain. Repeated microbiological analysis carried out after receiving probiotics, found marked statistically significant positive trend in the majority of patients (table 3-6).

So, in patients of all groups, indexes of the indigenous intestinal flora, *lactobacilli* and *bifidobacteria,* showed a general tendency to restore their normal amount and concentration of *E.coli* in 85-92% of patients returned to normal. In addition, all groups showed complete suppression of the number of conditionally pathogenic microflora (*S. saprophyticus, S. epidermidis, C. albicans, Cl. perfringens*), while the number *of S. aureus* in group II (7%) and III (6%) became 10^2 CFU/g.

None of the patients resulted in side effects of taking probiotics or allergic reactions.

DISCUSSION

Microbiological study of intestinal contents in patients of all groups showed significant changes in qualitative and quantitative composition of gut flora in patients with chronic inflammatory processes of different localization.

Chronic inflammation is accompanied by a sharp decline in the number of major symbionts of the colon (*Bifidobacterium, Lactobacillus, Escherichia coli,* and others.), as well as an increase in the number of conditionally pathogenic microflora (*S. aureus, S. saprophyticus, S. epidermidis, C. albicans, Cl. perfringens*).

The importance of the intestinal microbiome for a healthy body and in diseases is becoming increasingly clear as a result of study of the "body" and its changes in various diseases.

The major microbial community that lives in the gut, provides host defense against pathogens, helps digestion and absorption of nutrients and trace elements, the production of vitamins, neutralization of toxins, and the formation of the immune system.

Changes in the composition or the function of the microbial ecosystem called dysbacteriosis have been shown at a plurality of diseases such as atherosclerosis, obesity, metabolic syndrome, allergy, diabetes and inflammatory bowel disease, infections and other diseases [17,18]. At the same time, the intestinal flora of critically ill patient changes considerably as a result of reduced number of obligate anaerobes, *Bifidobacterium* and *Lactobacillus,* while the number of *Pseudomonas* and *Staphylococcus* increases, and this coincides with our results [19]. According to the researchers, the mechanism of changes in the gut flora in case of serious inflammation is a violation of the intestinal mobility (peristalsis) [8,19]. The newly proposed model assumes that the composition and spatial distribution of intestinal microflora is regulated independently from the

Table 1. Demographic characteristics of the study groups

Indicator	Group I n=58	Group II n=56	Group III n=48	Group IV n=40
Age (years, *M* ± *SD*)	31,5±6,3	29±8,4	37±11,2	35,65±8,2
Sex n/%– female	32 / 55%	39 / 70%	26 / 54%	27 / 67,5
– male	26 / 45%	17 / 30%	22 / 46%	13 / 32,5
Blood CD4 cell count (cells/μl), (n=40)				426±264
<350 cells /μl				223±99
>350 cells /μl				462±280

M – averages, SD –standard deviation

Table 2. Dynamics of clinical symptoms before and after correction of probiotics

Symptoms	Before correction (n/ M ±SD) n=162	After correction (n/ M ±SD) n=162
Abdominal pain	98 (60,4±3,87)	41 (25,3±5,3)*
Diarrhea or (stool frequency > 3 times a day	57 (35±4,9)	6 (3,7±6)*
Stool retention	74 (45,6±4,9)	5 (3±7,6)*
Nausea and loss of appetite	47 (29±6,6)	19 (11,7±7,3)**
Flatulence	94 (58±3,4)	23,4±5,3)*

* p<0,001; ** p>0,05

Table 3. Fecal flora in patients with respiratory system diseases before and after correction of probiotics (n=58)

Covariates	Fecal flora before correction		Fecal flora after correction		Normal
	log_{10}CFU/g	n	log_{10}CFU/g	n	
Bifidobacterium spp.	5.0 ± 0.6* 5.9 ± 0.8*	45 13	5.0 ± 0.6 7.7 ± 1.02	9 49	9.6 ± 0.7
Lactobacillus spp.	4.0 ± 0.5 7.0 ± 0.9	45 13	5.0 ± 0.6 7.0 ± 0.9	25 33	7.7 ± 1.2
E. coli (lac+)	5.0 ± 0.9* 5.0 ± 0.9*	29 29	5.9 ± 0.8 8.0 ± 1.06	5 53	8.0 ± 1.3
E. faecalis	5.0 ± 1.08* 7.0 ± 1.1*	21 37	5.9 ± 1.9 7.0 ± 1.0	9 49	7.74 ± 1.2
E. faecium	5.0 ± 0.6*	58	5.0 ± 1.4 7.4 ± 0.9	13 45	7.7 ± 1.2
E. coli Hly	ND	58	ND	58	ND
S. aureus	5.0 ± 1.9 5.9 ± 2.4 ND	7 6 45	ND ND	58	2.7 ± 0.8
S. epidermidis	4.0 ± 1.4 ND	8 50	ND	58	4.0 ± 0.6
S. saprophyticus	4.0 ± 1.4 4.0 ± 1.4	8 50	ND	58	4.0 ± 0.6
Candida spp.	4.0 ± 1.9 7.0 ± 1.9 ND	4 4 50	ND	58	2.0 ± 0.5
Cl. perfringens	5.9 ± 1.9 ND	4 54	ND	58	2.1 ± 0.7

damaging inflammation trigger [20]. Inflammation results in a progressive reduction of microbial diversity, transition from >95% of Gram-positive bacteria (*Firmicutes*) to >95% of Gram-negative bacteria (*Proteobacteria*) and translocation through the mucosa of such invasive bacteria as adherent-invasive *E. coli* or *Salmonella*.

Table 4. Fecal flora in patients with diseases of urogenital system (n=56)

Covariates	Fecal flora before correction		Fecal flora after correction		Normal
	log_{10}CFU/g	n	log_{10}CFU/g	n	
Bifidobacterium spp.	5.0 ± 0.7 5.9 ± 1.06	52 4	5.0 ± 1.02 7.0 ± 0.9	24 32	9.6 ± 0.7
Lactobacillus spp.	2.0 ± 0.3* 5.0 ± 0.7* 7.0 ± 0.9*	32 8 16	2.0 ± 0.3 7.0 ± 1.3 5.0 ± 0.9	0 28 28	7.7 ± 1.2
E. coli (lac+)	5.0 ± 1.3* 7.0 ± 1.9* 8.0 ± 1.4*	16 8 32	5.9 ± 1.8 7.0 ± 1.7 8.0 ± 1.4	8 16 32	8.0 ± 1.3
E. faecalis	4.0 ± 0.5* 7.0 ± 2.2*	46 10	5.9 ± 0.9 7.0 ± 1.5	36 20	7.74 ± 1.2
E. faecium	2.0 ± 0.4* 5.0 ± 1.1* 5.9 ± 1.1*	28 20 8	5.0 ± 0.9 5.9 ± 1.7 7.0 ± 1.8	28 12 16	7.7 ± 1.2
E. coli Hly	ND	56	ND	56	ND
S. aureus	ND 4.0 ± 0.5* 5.9 ± 0.8*	8 8 40	2.0 ± 1.9 ND ND	4 52	2.7 ± 0.8
S. epidermidis	ND	56	ND	56	4.0 ± 0.6
S. saprophyticus	ND	56	ND	56	4.0 ± 0.6
Candida spp.	ND	56	ND	56	2.0 ± 0.5
Cl. perfringens	ND	56	ND	56	2.1 ± 0.7

Table 5. Fecal flora in patients with pyoinflammatory postoperative complications (n=48)

Covariates	Fecal flora before correction		Fecal flora after correction		Normal
	log_{10}CFU/g	n	log_{10}CFU/g	n	
Bifidobacterium spp.	5.0 ± 0.7 7.0 ± 0.9	45 3	5.0 ± 0.9 8.0 ± 1.6	24 24	9.6 ± 0.7
Lactobacillus spp.	5.0 ± 0.7* 7.0 ± 0.9*	45 3	5.0 ± 0.8 7.0 ± 1.7	30 18	7.7 ± 1.2
E. coli (lac+)	5.0 ± 0.9* 7.7 ± 1.6*	24 24	5.9 ± 1.4 8.0 ± 1.2	6 42	8.0 ± 1.3
E. faecalis	5.0 ± 0.8 7.0 ± 1.4	42 6	5.0 ± 0.9 7.7 ± 1.6	27 21	7.74 ± 1.2
E. faecium	5.0 ± 1.4 7.0 ± 1.2	12 36	7.0 ± 1.9 7.7 ± 1.3	12 36	7.7 ± 1.2
E. coli Hly	ND	58	ND	58	ND
S. aureus	7.0 ± 1.9* ND	3 45	2.0 ± 1.6 ND	3 45	2.7 ± 0.8
S. epidermidis	ND	48	ND	48	4.0 ± 0.6
S. saprophyticus	ND	48	ND	48	4.0 ± 0.6
Candida spp.	4.0 ± 0.9 5.9 ± 1.6 ND	14 14 20	2.0 ± 0.4 ND	25 23	2.0 ± 0.5
Cl. perfringens	5.9 ± 1.8 ND	3 45	ND	48	2.1 ± 0.7
P. aeruginosa	5.9 ± 1.8 ND	3 45	ND	48	2.8 ± 1.4

Table 6. Fecal flora in HIV-1 infected patients before and after the correction of probiotics

Covariates	Fecal flora before correction		Fecal flora after correction		Normal
	log_{10}CFU/g	n	log_{10}CFU/g	n	
Bifidobacterium spp.	5.9 ± 0.9* 7.0 ± 1.1*	36 4	5.9 ± 1.4* 8.0 ± 1.8	19 1	9.7 ± 1.4
Lactobacillus spp.	5.0 ± 0.8* 6.7 ± 1.07*	35 5	5.0 ± 1.1* 7.7 ± 1.7	12 8	7.7 ± 1.2
E. coli (lac+)	5.9 ± 1.2* 8.7 ± 1.4	24 16	8.7 ± 1.9	20	8.0 ± 1.3
E. faecalis	5.0 ± 1.02* 7.7 ± 0.8	25 15	5.0 ± 1.1* 7.7 ± 1.7	6 14	7.74 ± 1.2
E. faecium	5.0 ± 0.8* 5.9 ± 0.9*	34 6	5.0 ± 0.9*	20	7.7 ± 1.2
E. coli Hly	ND 5.0 ± 0.9*	2 38	ND 5.0 ± 1.1*	19 1	ND
S. aureus	ND 4.0 ± 1.6	33 7	ND	20	ND
S. epidermidis	4.0 ± 0.8 5.0 ± 1.4	27 13	ND	20	4.0 ± 0.6
Candida spp.	2.9 ± 0.5 4.0 ± 1.5*	32 8	ND	20	4.0 ± 0.6
Cl. perfringens	2.0 ± 0.3 2.9 ± 0.4	38 2	2.0 ± 0.5 2.9 ± 0.7	16 4	2.9 ± 0.5

Specific factors associated with inflammation, which cause dysbacteriosis, remain unclear. Perhaps the basis of dysbiosis are perturbations in the microenvironment, such as increased accessibility of the substrate for the growth of Gram-negative bacteria (for example, iron and serum, increased number of dead or dying cells) and loss of substrates for Gram-positive flora (for example, the mucus of goblet cells). Genetic susceptibility seems to affect the threshold of dysbiosis in response to an external trigger, as well as the ability to control the self-reinforcing cycle of dysbacteriosis/inflammation. Our studies have shown that probiotics proved to be safe and quite effective correction of dysbiotic disorders associated with chronic inflammation. The use of probiotics resulted in clinically significant results, but the bacteriological changes were not associated with all the important species of bacteria, and not all cases were statistically significant. Probiotics are generally defined as live microbes which, when taken in adequate amounts, confer a health benefit to the person taking them. The criteria for the use of commensal species as probiotics are human origin, acid resistance, and survival during the transition through the gastrointestinal tract, the lack of pathogenicity, production of antimicrobial substances (bacteriocins), modulation of immune activity [21]. Lactic acid bacteria (*lactobacilli* and *bifidobacteria*) are most commonly used as probiotics that do not cause inflammatory reactions. However, other bacteria, including pathogenic *E.coli,* yeast, especially *Saccharomyces boulardii*, and multi-view cocktails are also used as probiotics. The number of components of such drinks may be more than 30 species, including *Lactobacillus casei, L. plantarum, L. acidophilus, L. delbrueckii subspecies bulgaricus, Bifidobacterium infantis, B. breve, B. longum*, and *Streptococcus salivarius* of subspecies *thermophilus*. Fermented dairy products enriched by probiotic bacteria are a good example of functionally oriented products. Annual sales of such beverages in Europe exceed 1.2 bln. euro [22]. The use of probiotics has a major beneficial effect not only on the accompanying dysbiosis, but also on the underlying disease, including critical conditions.

Thus, a 4-8 week course of taking probiotic strain of *Lactobacillus* GGAT 53103 in case of liver cirrhosis accompanied by hepatic encephalopathy resulted in reduced endotoxemia and normalization of intestinal microbial scenery without any side effects [23]. The use of two probiotic strains of *Bifidobacterium breve BR03* and *B. breve B632* inhibited production of proinflammatory cytokine TNF-α in children with celiac disease [24]. Probiotic preparation containing *Lactobacillus ±±paracasei CRL-431, Bifidobacterium BB-12* and *Streptococcus thermophilus TH-4*, decreased the number of *Clostridium spp*. and production of secretory IgA with simultaneous increased content of *bifidobacteria* and *lactobacilli* in children with recurrent respiratory tract infections [25].

Therefore, our research and the study of other authors give grounds to assert that the probiotic preparations are a powerful tool for the normalization of intestinal flora at dysbiosis of various origins and can be added to basic therapy.

CONCLUSIONS

Intestinal disorders in patients with chronic inflammation saw a decrease the number of colon symbionts and reduc-

tion its protective properties that accompanied the advent of pathogenic microorganisms. Probiotics demonstrated statistically significant improvements in the qualitative and quantitative composition of gut flora.

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INFLUENCE OF VARIANTS CIRCADIAN RHYTHM OF BLOOD PRESSURE ON THE FUNCTIONAL STATE OF THE CARDIOVASCULAR SYSTEM IN PATIENTS WITH ESSENTIAL HYPERTENSION II DEGREE

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ABSTRACT

Introduction: Blood pressure is chronic disease in which the main diagnostic feature (symptom) is a persistent increase in hydraulic pressure in the arterial vessels of the large circulatory system. Increased blood pressure causes the heart to work with greater load due to increased general peripheral vascular resistance to ensure normal blood circulation in the blood vessels of the large circulatory system.

The aim of our work was to detection of features of the functional state of the cardiovascular system in patients with essential hypertension II degree depending from the circadian structure of blood pressure.

Materials and methods: The complex examination of 62 patients with essential hypertension II degree with II-III degree by increase of blood pressure. The average age of patients was - 56.2 ± 2.1 years. There were examined the 36 men and 26 women. All 62 patients with essential hypertension of IInd stage with II-III degree of blood pressure increase were divided into 3 groups due to the circadian structure of blood pressure: « Dipper» -26; «Non dipper»-28; and «Night picker» -8.

Results and conclusions: In patients with the daily index "Dipper" the normokinetic range of hemodynamics prevails, make a difference to patients with "Non dipper" and "Night picker", which has a mainly hypokinetic range of hemodynamics, which is confirmed by ratios of indicators to the area and weight of the body of the subjects. In addition to holding parallels between the body mass index and the left ventricular mass index enables that the increase in inconsistency of the body mass index to the left ventricular myocardial mass index, which deepens in groups from "Dipper" to "Night Picker", can increase the metabolic imbalance of the myocardium.

KEY WORDS: heart, blood vessels, blood pressure

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INTRODUCTION

Blood pressure is chronic disease in which the main diagnostic feature (symptom) is a persistent increase in hydraulic pressure in the arterial vessels of the large circulatory system. Increased blood pressure causes the heart to work with greater load due to increased general peripheral vascular resistance to ensure normal blood circulation in the blood vessels of the large circulatory system. Two indicators are used to measure blood pressure: systolic and diastolic pressure, depending on whether the heart muscle is contracted between strokes (systole) or relaxed (diastole). Normal blood pressure at rest is in the range of 100-139 mm Hg. systolic pressure (upper value) and 60-89 mm Hg diastolic pressure (lower value). Blood pressure is considered high if it is constantly at 140/90 mm Hg. or higher. The treatment of hypertension may be successful for a perfect diagnosis of the passing by disease. It is known that for circadian rhythm, the blood pressure of patients with hypertension is distributed for «dipper» and «non dipper» - with a low and negative daily index in accordance, «Non dipper» and «Night picker». The last two forms of the daily structure of blood pressure are defined by the majority of clinicians as more aggressive, resistant to treatment options for the course of hypertension. [1.2, 3, 4].

Research for the features of the functional state of the cardiovascular system in patients with essential hypertension II degree depending on the circadian structure of blood pressure, it was found that the main ranges of the central (cardiac) hemodynamics in these groups are not definitely. In patients with the daily index «Dipper» the normokinetic range of hemodynamics prevails, make a difference to patients with «Non dipper» and «Night picker», which has a mainly hypokinetic range of hemodynamics, which is confirmed by ratios of indicators to the area and weight of the body of the subjects. In addition to holding parallels between the body mass index and the left ventricular mass index enables that the increase in inconsistency of the body mass index to the left ventricular myocardial mass index, which deepens in groups from «Dipper» to «Night Picker», can increase the metabolic imbalance of the myocardium [5].

We know that prolonged, constant loading the blood pressure in the day and night periods of the day causes progressive hypertrophy of the left ventricle, changes the structure and function of the blood vessels. [6,7,8,9]. There is not enough information about the degree of left ventricular hypertrophy and the state of resistive blood vessels in

patients with essential hypertension in II-III degree for a variants of circadian structure of the blood pressure, features of blood distribution into the arterial and venous channels, the correlation of durability arterial and venous vessels [10,11,12,13].

THE AIM

The aim of our work was to detection of features of the functional state of the cardiovascular system in patients with essential hypertension II degree depending from the circadian structure of blood pressure.

MATERIALS AND METHODS

All studies conducted at the Department of Nursing Higher State Educational Institution of Ukraine "Bukovinian State Medical University", for 2016 -2019 years.

During the complex examination of 62 patients with essential hypertension II degree with II-III degree by increase of blood pressure. The average age of patients was - 56.2 ± 2.1 years. There were examined the 36 men and 26 women.

All 62 patients with essential hypertension of IInd stage with II-III degree of blood pressure increase were divided into 3 groups due to the circadian structure of blood pressure: « Dipper» -26; «Non dipper»-28; and «Night picker» -8.

The exclusion criteria were: the age of patients to 20 and over 75 years of age, the evidence of hard forms the heart failure II-B, III degree, passed the acute myocardial and coronary circulatory disorders, and oncological diseases.

The all patients were examined by daily monitoring of blood pressure by hardware « Solvaig» with the appropriate software. According to the protocol of research, the average daily, night and daily blood pressure, its average dynamic value for the same periods was determined.

In addition, all patients were given an ultrasound examination of the heart using the "En visor" device. 56 patients of them of central venous pressure was determined by the classical method using the Waldman apparatus.

The value of total peripheral vascular resistance was counted by the modified Poiseuil formula.

Research was perfomed to according with basic bioethical requirements and fundamental guidelines for clinical research.

RESULTS AND DISCUSSION

It was found that the basic parameters of the central (cardiac) hemodynamics in the mentioned groups are not unambiguous. Patients with the daily index «Dipper» had the prevalence of normokinetic type of hemodynamics, in contrast to patients with «Non dipper» and «Night picker», who had predominantly hypokinetic type of hemodynamics, which is confirmed by ratios of these indicators to the body surface and weight. The steady high daily average level of blood pressure in «non-dippers» patients, especially in «Night pickers», contributes to the formation of a high baseline level of general peripheral vascular resistance with adaptation in these patients to the hypokinetic type of central hemodynamics. In addition, the parallels between the body mass index and the left ventricular mass index suggest the increase of mismatch between body mass index and left ventricular mass index, which might aggravates from «Dipper» to «Night pickers», which can exacerbate the metabolic imbalance of the myocardium. Analysis of the central venous pressure indices by the circadian rhythm of blood pressure suggests that a large proportion of patients with low and negative daily index arterial hypertension is combined with venous hypertension, which results in changes in pathogenetic approaches to successful antihypertensive treatment.

Comparison of cardiac hemodynamics with mean values of blood pressure according to daily blood pressure monitoring are presented in Table I.

From the tables 1 data in patients with essential hypertension of stage II with II-III degree of ambulant blood pressure distribution divided into groups according to the main characteristic - the daily index according to the circadian rhythm, it was established that the parameters of intra cardiac hemodynamics are not unambiguous.

So, in patients with a rhythm of blood pressure - «Dipper» the highest indices of shock volume (shock index) and more significant integral magnitude - minute volume of blood (card index), indicating the advantage of most patients in this group of normokinetic version of central hemodynamics.

In patients with the same stage of the disease with daily rhythms - «Non dipper» and «Night piccher», absolute average values of shock volume and minute volume of blood though fluctuate within the limits of the physiological norm, but counted by the area of the body - significantly and significantly lower than the data the group «Dipper», especially in patients with a version of the daily index - «Night Picker».

Probably, most of them form a hypokinetic version of the blood flow.

According to the integral value of blood pressure - midnight - night and day, daily average hemodynamic blood pressure, in patients with a daily rhythm of blood pressure «Dipper» these values are approaching normal with a tendency to increase in the inverse relationship with the value of the daily index.

The fact is interesting, there is a significant increase in the night-time rate of average daily pressure in patients with the «Night Picker» group compared to daily amount. With objective values of cardiac activity and average blood pressure levels, it is possible to counted the total peripheral vascular resistance, one of the 3 main parameters of blood pressure (minute volume of blood (card index) ↔ the circle of blood circulating ↔ total peripheral vascular resistance, according to the modified Poiseuil formula.

From the data obtained, it can be seen that the overall peripheral vascular resistance of patients with non dipper groups, and especially the «Night Picker», is significantly different from patients with a daily rhythm «Dipper».

After analyzing the night total peripheral vascular resistance, taking into account the average daily value of minute

Table I. The main values of central (cardiac) hemodynamics and peripheral vascular resistance in patients with essential hypertension II degree active variants of the daily structure of blood pressure.

№	DI, %	SVB ml	SI ml/m²	MVB l/m	CI l/m /m²	ABP daily mm Hg	ABP day mm Hg	ABP night mm Hg	TPVR daily	TPVR day	TPVR night	ΔTPVR day - night
1	D 10-20% n=26	87,3± 5,77	44,8 ± 1,40	6,5± 0,45	3,36± 0,110	100,6± 2,19	102,2± 3,41	87,7± 3,13	1232± 101	1261± 98	1102± 92	Δ159
2	ND 0-10% n=28	71,7± 5,47	36,7± 1,60	5,6± 0,47	2,90± 0,120*	102,9± 2,81	103,5± 3,11	92,2± 3,9	1487± 104	1482± 101	1328± 98	Δ154
3	NP 0-(10)% n=8	63,3± 6,80*	31,4± 1,80*	4,6± 0,50*	2,28± 0,100*	103,1± 2,23	105,5± 3,30	98,3± 3,36*	1802± 120*	1843± 106*	1734± 108*	

*- values that are significantly different from the "Dipper" group.

Table II. The value of the parameters, mass of the left ventricle and central venous pressure in patients with essential hypertension II degree

№	DI, %	S (m²)	BMI w/m²	CVP mm. H_2O	TIM s (s)	TLWLV s (s)	TIM d(s)	TLWLV d(s)	MLVM w	LVMI w/m²	BMI / LVMI
1	D 10-20% n=26	1,95± 0,11	29,92± 2,36	129,9± 12,0	1,40± 0,07	1,42± 0,08	1,19± 0,06	1,20± 0,07	230,2± 3,82	120,6± 1,22	206,7± 1,19
2	ND 0-10% n=28	1,94± 0,10	30,67± 2,28	145,9± 16,2	1,49± 0,08	1,65± 0,09	1,29± 0,05	1,21± 0,05	241,2± 3,90	125,0± 1,28	245,4± 1,24*
3	NP 0-(-10)% n=8	2,02± 0,13	31,27± 2,49	160,6± 5,8*	1,49± 0,05	1,68± 0,09*	1,30± 0,04	1,25± 0,06	261,8± 4,14*	130,2± 1,52*	240,2± 1,16*

* - values that are significantly different from the "Dipper" group.
TIM - thickness of the interventricular membrane
TLWLV - thickness of the left wall of the left ventricle

volume of blood, reliable differences were found between the high total peripheral vascular resistance compared with the relatively low and close to norm in patients with circadian rhythm «Dipper».

The obtained data confirm the preliminary assumption that in patients with essential hypertension of stage II with daily rhythms, «non-dipers», the variant of the cardiac (central) hemodynamics is transformed from the normokinetic in «dipers» to the hypokinetic variant (in «non dipers» - «non dipper» and «Night Picker»). The consistently high total peripheral vascular resistance during the day results in an adaptive reaction of cardiac hemodynamics with low kinetic properties in patients with predominantly low and negative daily odds, «Non dipper» and «Night piccher».

From the tables 2 data, the mean values of central venous pressure in direct dependence on the average daily average daily pressure (Table I) with a tendency to increase in patients with the group «Non dipper» and significantly increased in patients with a daily rhythm «Night picker».

If the central venous pressure o in patients with the group «Non dip1per» is slightly higher than normal (60-120 mm H2O), then in patients with the group «Night Picker» - almost 2 times higher than normal.

So, the variant of the course of arterial hypertension is combined with venous arteriovenous hypertension. Consequently, the increased manifestations of the hypokinetic variant of central hemodynamics in patients with essential hypertension of stage II with a low and negative daily index («Non dipper», «Night picker») forms arterial venous hypertension, which causes changes in pathogenetic approaches to successful antihypertensive treatment.

An important, in our opinion, is the analysis and implementation of parallels between the body mass index and the structural changes in the left ventricular myocardium, depending on the daily rhythm of arterial pressure in these patients. From tabl. 2 it is seen that in all groups of patients there is a hypertrophy of the left ventricle, more pronounced back wall of the left ventricle with a significant increase in «not Dipers». The diastolic size of the posterior wall and the interstitial membrane of the patients was reliable and did not reveal any changes.

The mass of the left ventricular myocardium and its index grew in inverse dependence on the magnitude of the daily

index. The working hypertrophy of the left ventricular wall and left ventricular myocardial mass did not have a clear interpretation in relation to the body mass index.

Accordingly, we can conclude that the incidence of inconsistency of the body mass index in patients with different groups of daily indices with left ventricular mass index, which deepens from Dipper to Non dipper and Night Picker, can be concluded. Consequently, in patients with «non-Dipers», the deficit of the left ventricular mass of the body increases, which can increase the metabolic imbalance of the myocardium and its functional incompatibility.

Therefore, with the distribution of 62 patients with essential hypertension of the second stage with II-III degree of blood pressure increase in circadian structure of arterial pressure in 3 groups: «Dipper» -26; Non dipper -28; and «Night picker» -8, found that the basic parameters of the central (cardiac) hemodynamics in the specified groups are not unambiguous. In patients with the daily index «Dipper» the normokinetic variant of hemodynamics prevails, in contrast to patients with «Non dipper» and «Night picker», which has a predominantly hypokinetic variant of hemodynamics, which is confirmed by ratios of indicators to the area and weight of the body of the subjects.

The steady high daily average level of arterial pressure in patients with non-Dipers, especially, «Night Picker», contributes to the formation of a high baseline level of the general peripheral vascular resistance with adaptation in these patients to the hypokinetic variant of central hemodynamics. In addition, the parallels between the body mass index and the left ventricular mass index suggest that the increase in inconsistency of the body mass index to the left ventricular myocardial mass index, which deepens in groups from Dipper to Night Picker, can increase the metabolic imbalance of the myocardium .

Analysis of data on the determination of central venous pressure for circadian rhythms of arterial pressure suggests that in a significant proportion of patients with a low and negative daily index, arterial hypertension is combined with venous hypertension, which leads to changes in pathogenetic approaches to successful antihypertensive treatment.

CONCLUSIONS

1. Patients with essential hypertension of IInd stage («Non dipper» and «Night picker») mostly have the hypokinetic type of cerebral hemodynamics with high general peripheral vascular resistance and low kinetic properties of cardiac hemodynamics.
2. Patients with low and negative daily index of circadian blood pressure structure - «Non dippers» and «Night pickers» have a higher degree of left ventricular wall hypertrophy and increasing incongruence of the left ventricular myocardial mass index to the body weight index with ticiency of the myocardial mass to the body mass, which can increase the metabolic imbalance of the myocardium.
3. According to the type of essential hypertension stage II, patients with circadian rhythm blood pressure - «Non dipper» and, especially, «Night picker»-arterial hypertension are combined with venous (AVH), respectively, in 46% and 80% of cases, compared with 'Dipper' - 40%, which possibly causes an increase in number of treatment-resistants, acceleration of essential hypertension progressions.

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REVIEW ARTICLE
PRACA POGLĄDOWA

EPIDEMIOLOGY OF DISEASES OF THE CIRCULATORY SYSTEM AMONG THE POPULATION OF POLTAVA REGION

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ABSTRACT

Introduction: In Ukraine more than half of deaths have been caused by cardio-vascular diseases (CVD). Among the able-bodied population, the share of CVD in the structure of causes of mortality is 29,9%. In the structure of causes of mortality among the persons of retirement age, CVDs accounted for 75,9% and exceeded the proportion of neoplasms in 6,5 times.

The aim is to analyze of morbidity and mortality rates of diseases of the CVD among the population of Ukraine and Poltava region, to conduct a comparative analysis of data to identify possible ways to improve the situation.

Materials and methods: A retrospective study of morbidity and mortality rates by age, gender and cause (2014-2018) was conducted and the statistical method was used to analyze dynamic (time) series.

Review: An analysis of the dynamics of population mortality indicates significant fluctuations in it`s levels over ten years. At the same time, by the method of alignment of the dynamic series, a tendency to a slight decrease in the mortality rate of the population from 17,1‰ to 16,9 ‰ was established. The mortality of the population of Ukraine in 2018 from diseases of the circulatory system was 1000,8 per 100 thousand people. Data on mortality rate in the Poltava region significantly higher than those in Ukraine.

Conclusions: The age structure of the population of Poltava region belongs to the regressive type. The mortality rate among the population of Poltava region is slightly decreasing but remains at a very high level (16,9 ‰). In the structure of causes of death, diseases of the circulatory system are at the first place (70,8%), the second place belongs to neoplasm (13,5%), and third are the external causes of death (4,8%).

KEY WORDS: population health statistics, epidemiology, circulatory system diseases, myocardial infarction

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INTRODUCTION

According to data from the World Health Organization, there is 17 million people die annually from the circulatory disease and by 2030 this indicator` level will be about 23,3 million in a year mainly from heart disease and stroke, which are projected to remain the only major causes of death [1].

The main oriented target of policy "Health 2020" in Europe is the annual reduction in the indexes of untimely mortality on the 1,5% for four groups of causes: cardiovascular diseases (CVD), malignancies, diabetes and chronic respiratory diseases [2].

The tasks set out in the document "Health-21. The basics of health policies for all in the WHO European Region" aimed at addressing cardiovascular disease-related mortality reductions in people under 65 by an average of 40% [3].

In the countries of the European Region (26 countries) life expectancy at birth according to WHO is more than 75 years, while in Ukraine, according to the National Bureau of Statistics (2017), the estimated life expectancy was 71,98 years.

Studies on the health of the population, including the spread of diseases of the circulatory system, are devoted to a number of works that indicate an unsatisfactory epidemic situation [4, 5, 6, 7].

In Ukraine, since the middle part of 1970s and till the present time, more than half of deaths have been caused by cardio-vascular diseases (CVD). Among the able-bodied population, the share of CVD in the structure of causes of mortality is 29,9%. In the structure of causes of mortality among the persons of retirement age, CVDs accounted for 75,9% and exceeded the proportion of neoplasms in 6,5 times [8].

Also, it should be noted that diseases of the circulatory system occupy the first rank place among causes of disability in the adult population (23,1%) and the second place (22,6%) among the able-bodied population - according to Ipatov AV et al. (2018) [9].

Nowadays there is a lot of knowledge that is needed for the prevention, diagnosis and treatment of diseases of the cardiovascular system, but the analysis of the situation allows us to conclude that the existing methods are not always effective. The Institute for the Measurement of Health and Health Assessment through DALY calculates that in Europe 60% of the burden of disease is accounted by seven leading risk factors: high blood pressure, smoking, alcohol abuse; high cholesterol content in the blood; overweight; low consumption of fruits and vegetables; sedentary lifestyle [10].

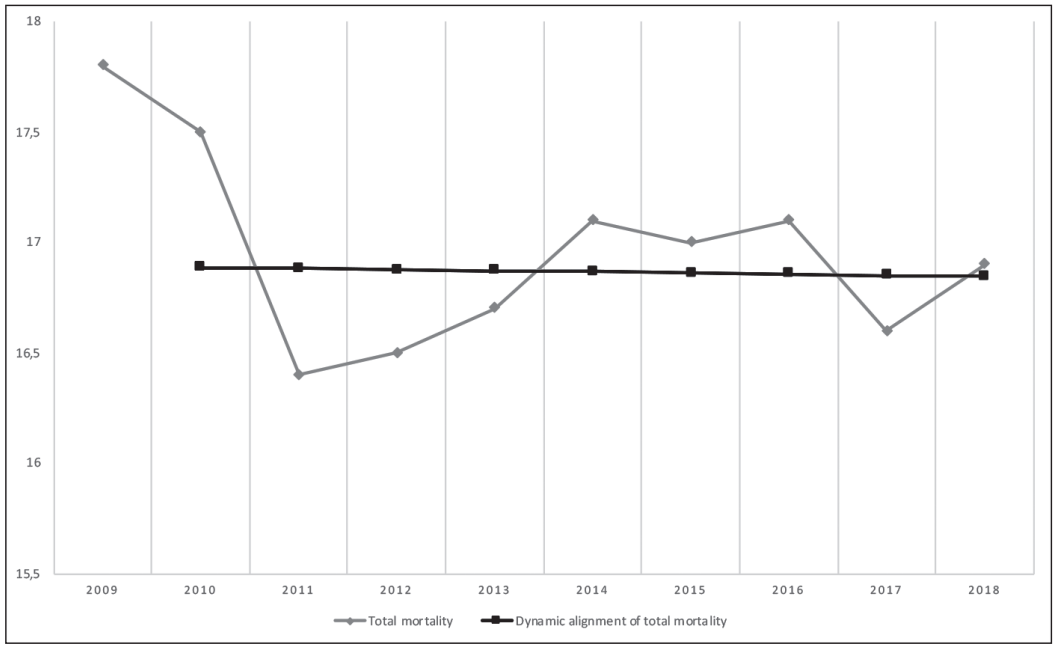

Fig. 1. Dynamics of mortality rate in population of Poltava region (‰) in a period of 2009-2018 years.

The leading role in shaping the burden of disease and mortality in the countries of the WHO European Region play cardiovascular diseases, malignant neoplasms, chronic obstructive pulmonary disease, diabetes and risk factors for their development, they should be monitored and the object of attention of executives and health professionals, people who make decisions.

The study of the prevalence of diseases of the cardiovascular system, including myocardial infarction, and their impact on untimely mortality rates in Ukraine, should provide a basis for deliberate policy development for public health.

THE AIM

The main task is to analyze the dynamics of morbidity and mortality rates of diseases of the circulatory system among the population of Ukraine and Poltava region, to conduct a comparative analysis of data to identify possible ways to improve the situation.

MATERIALS AND METHODS

The materials of this study were the materials of the State Statistics Service of Ukraine, the data of the Public Enterprise "Poltava Regional Information and Analytical Center of Medical Statistics of the Poltava Regional Council", as well as the "Health for All" Database (HFA-DB) was used. A retrospective study of morbidity and mortality rates by age, gender and cause (2014-2018) was conducted. During the study, biblio-semantic and information-analytical methods were used, and the statistical method was used to analyze dynamic (time) series.

REVIEW AND DISCUSSION

According to the census which were conducted in 2001, the population of Poltava region was 1630,1 thousand inhabitants, including urban population – 956,7 thousand people (58,7%), rural population – 673,4 thousand people (41,3%); it is also known that 45,9% were male, 54,1% were female. As of January 1, 2019, the permanent population of the Poltava region is 1392,6 thousand people, and compared to 2001, the population decreased by 247 800 people (15,1%). According to estimated data, the urban population is 861400 people, which is 61,8%, and the rural population - 531201 people (38,2%).

The demographic situation of the Poltava region is by many features typical for all agrarian and industrial regions of Ukraine. In the last decade, negative indicators of population reproduction have characterized it.

The age structure of the population of the region refers to the regressive type. The share of persons aged 60 years and over is 24,3%, while the share of persons from 0 to 14 years is 14,2%. And it should be noted that the share of persons over 60 years is constantly changing. According to the 2001 census, the share of people over 60 in the Poltava region was 24,1%, in 2009 it was 22%, and in 2019 it was already 24,3%.

An analysis of the dynamics of population mortality indicates significant fluctuations in levels over ten years. At the same time, by the method of alignment of the dynamic series, a tendency to a slight decrease in the mortality rate of the population from 17,1 ‰ to 16,9 ‰ was established (Fig.1).

Traditionally, in the hierarchy of death causes of the population of Ukraine, the first five places consisted of the following classes of causes: diseases of the circulatory system, neoplasms, external causes of death, diseases of the digestive system and diseases of the respiratory system.

There is a certain difference in mortality rates across age and gender groups. Naturally, mortality from circulatory system diseases is higher among men in all age groups. Mortality rates are equal for men and women in the age group of 80 years and older.

Table 1. The level of mortality from diseases of the circulatory system among the population of Ukraine and Poltava region (per 100 thousand people)

	From diseases of the circulatory system (I00-I99)						
	Total	Including		Coronary heart disease (I20-I25)		Cerebrovascular disease (I60-I69)	
		M	W	M	W	M	W
Ukraine	1000,8	942,6	1051,4	652,9	733,9	164,8	197,0
Poltava region	739,6	1111,1	1219,9	772,8	831,3	251	320,5
Visibility index,%	118,4	121,0	117,6	121,3	115,1	154,5	164,5

Table 2. Analysis of the dynamics of the prevalence and incidence of diseases of the circulatory system among the population of Poltava region

Year	Prevalence				Incidence			
	Row level	Absol. growth	Visibility index	Growth rate	Row level	Absol. growth	Visibility index	Growth rate
2014	6378,9	-	100	-	382,9	-	100	-
2015	6507,4	128,5	102	2	408	25,1	106,6	6,6
2016	6494,1	-13,3	101,8	-0,2	420,3	12,3	109,8	3,0
2017	6623,6	129,5	103,8	2,0	411,9	-8,4	107,6	-2,0
2018	7745,6	1122	121,4	16,9	485,2	73,3	126,7	17,8

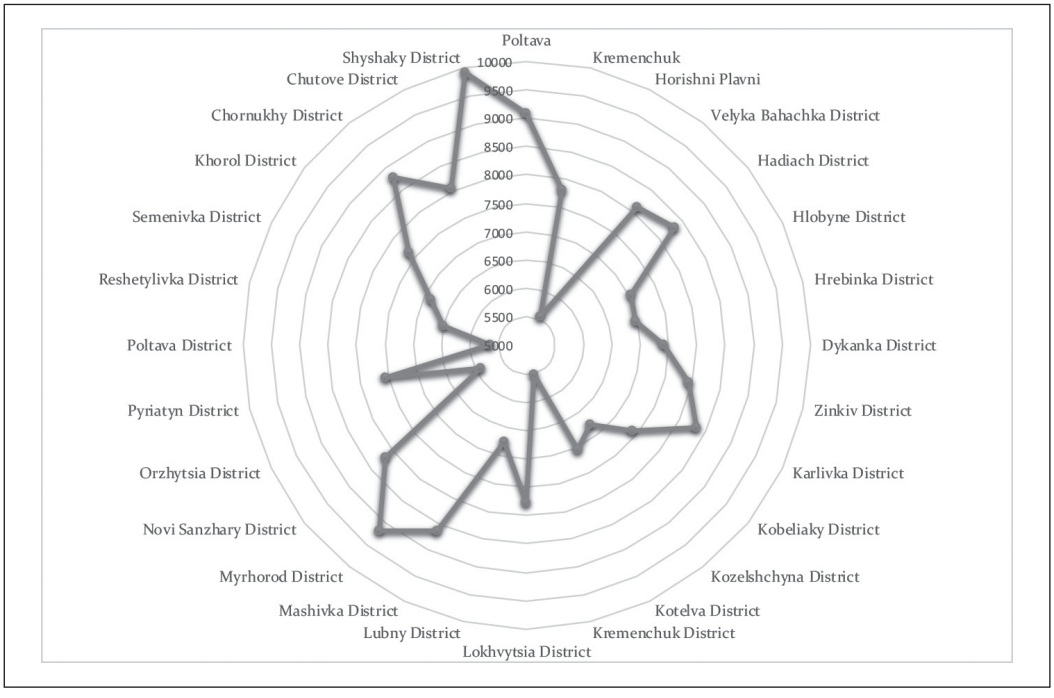

Fig. 2. Prevalence of circulatory system diseases in districts of Poltava region in 2018.

The mortality of the population of Ukraine in 2018 from diseases of the circulatory system was 1000,8 per 100 thousand people, including cases of coronary heart disease – 696,2, and cases of cerebrovascular disease – 182,0. The second largest cause of death is neoplasms – 201,2 per 100 thousand people. Third place among the causes of death of the population of Ukraine was held by external causes – 79,6 per 100 thousand people (Tab.1).

Data on mortality rate in the Poltava region significantly higher than those in Ukraine: overall mortality by 14%, mortality from coronary heart disease in men by 21,3% and women by 15,1%, cerebrovascular disease in men by 54% and women 64%.

Thus, in 2018, 70,8% (in 2014 – 69,5%) cases of deaths are caused by circulatory system diseases; 13,5% (in 2014 – 13,6%) of causes of death are neoplasms; 4,8% (in 2014 – 5,5%) of cases were caused by external causes; respiratory diseases accounted for 3,3% (3,3% in 2014) of deaths. The proportion of causes of death of digestive diseases decreases from 2,0% in 2014 to 1,2% in 2018.

An analysis of the incidence and prevalence rates of circulatory system diseases shows of the moderate fluctuations in the levels of these indicators, but the visibility indicator shows a 21,4% increase in circulatory system disease prevalence in 2018 compared to 2014. At the same time, there is a 26,7% increase in newly registered diseases.

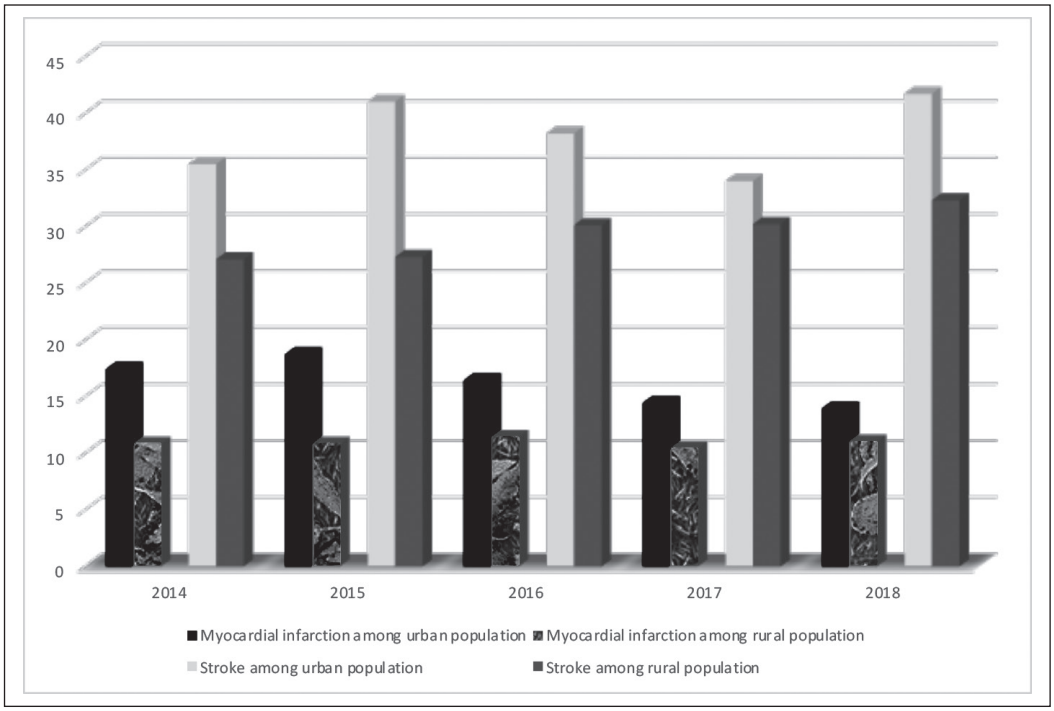

Fig. 3. Dynamics of myocardial infarctions and strokes among urban and rural population of Poltava region in a period of 2014-2018.

Table 3. Dynamics of the average duration of treatment and lethality of patients with diseases of the circulatory system in hospitals in Poltava region

Year	Diseases of the circulatory system		Coronary heart disease		Acute myocardial infarction		Cerebrovascular diseases	
	Average duration of treatment (days)	Lethality	Average duration of treatment (days)	Lethality	Average duration of treatment (days)	Lethality	Average duration of treatment (days)	Lethality
2014	11,0	4,8	11,0	4,7	13,6	17,0	10,1	8,8
2015	10,7	4,5	11,0	4,7	13,5	15,5	10,6	8,1
2016	10,5	4,9	10,7	5,2	11,6	13,9	10,3	8,1
2017	10,2	4,7	9,9	4,8	11,7	13,7	10,3	8,5
2018	9,9	5,1	9,7	5,3	11,5	14,0	10,2	8,1
In % to 2014	90,0	106,3	88,2	112,8	84,6	82,4	101,0	92,0

It is established that in comparison with 2014, the prevalence of circulatory system diseases is increasing (by 2,6% - among urban population; by 4,2% - among rural population). Primary morbidity rates have increased (by 3,4% among urban population, by 29,1% among rural population) (Tab.2).

Analysis of data by separate sidtricts of Poltava region indicates significant fluctuations in the prevalence of diseases of the circulatory system: the lowest indices in the Kremenchuk district (5525,6 per 10 thousand population) and in Horishni Plavni (5556,2 per 10 thousand population), the highest indicators in the Shyshaky district (9923,6 per 10 thousand population) and Myrhorod district (9181,6 per 10 thousand population) (Fig.2).

Analyzing the dynamics of myocardial infarction and stroke rates in the urban and rural population of Poltava region (2014-2018), we can conclude that the number of cases of myocardial infarction among the urban population of Poltava region compared with 2014 decreased by 20,11%, and among the rural population on the contrary, it increased by 1.85%. In turn, the increase in the number of strokes among the urban population by 17,46% and among the rural population by 19,9% is worrying (Fig.3).

An analysis of the dynamics of hospital morbidity show that the number of hospitalizations with diseases of the circulatory system has slowly tendency to decreasing, so in 2018 it`s level was on 49,4 per 100 thousand population (48,7 in 2014). The average duration of treatment for circulatory system diseases is reduced by 10%, with the mortality rate increasing by 6.3% in 2018 compared to 2014. The mortality rate from coronary heart disease has also increased by 12,8%. It should be noted that lethality rates from myocardial infarction are reduced by 17,3% and cerebrovascular diseases by 8% (Tab.3).

CONCLUSIONS

After the analyzing of the demographic indicators of the population of Poltava region, as well as the incidence of diseases of the circulatory system, we can make the following conclusions. The age structure of the population of Poltava region belongs to the regressive type. The mortality rate among the population of Poltava region is slightly decreasing but remains at a very high level (16,9‰). In the structure of causes of death, diseases of the circulatory system are at the first place (70,8%), the second place belongs to neoplasm (13,5%), and third are the external causes of death (4,8%). There is an increase in the incidence and prevalence levels of diseases of the circulatory system, mainly among the rural population. The incidence of myocardial infarction among the urban population decreased by 20,11%, while in the rural population it increased by 1,85%.

Indicators of mortality and morbidity of the population of Poltava region with circulatory system diseases are indicators of organizational accomplishments in the policy of preserving the health of the population. It is also the basis for further steps in the prevention of premature mortality and morbidity.

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REVIEW ARTICLE
PRACA POGLĄDOWA

ŻYWIENIE W WYBRANYCH CHOROBACH WIEKU PODESZŁEGO

NUTRITION IN SELECTED OLD AGE DISEASES

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STRESZCZENIE

W populacji Polski, podobnie jak i w innych krajach Europy, zachodzi proces starzenia się społeczeństwa. Przewiduje się, że w Polsce w 2050 roku nawet 35% społeczeństwa może być seniorami. Z wiekiem w organizmie zachodzą liczne zmiany, które powodują konieczność modyfikacji dotychczasowego sposobu odżywiania. Nieprawidłowa dieta jest czynnikiem ryzyka wielu chorób wieku podeszłego, do których należą: choroby neurodegeneracyjne, osteoporoza, miażdżyca, udar mózgu, cukrzyca typu 2 i nadciśnienie tętnicze. **Celem niniejszej pracy** jest przegląd zaleceń z zakresu żywienia w wybranych chorobach wieku podeszłego. Dieta seniorów powinna zapewniać odpowiednią ilość składników odżywczych i być dostosowana do występujących schorzeń. Odpowiedni sposób odżywiania może zmniejszyć ryzyko powikłań chorób starczych.

SŁOWA KLUCZE: dieta, żywienie, choroby wieku podeszłego

ABSTRACT

In the population of Poland, as well as in other European countries, an aging process is taking place. It is expected that in Poland in 2050, up to 35% of the population may be seniors. With increasing age, there are numerous changes in the body that necessitate the modification of the current diet. Incorrect diet is a risk factor for many old age diseases, including neurodegenerative diseases, osteoporosis, atherosclerosis, stroke, type 2 diabetes and hypertension. The aim of this study is to review the nutrition recommendations in selected diseases of the elderly. The diet of seniors should provide the right amount of nutrients and be adapted to existing diseases. A proper diet can reduce the risk of complications from senile diseases.

KEY WORDS: diet, nutrition, age-related diseases

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WSTĘP

Według Światowej Organizacji Zdrowia (WHO –– *World Health Organization*) seniorem można nazwać osobę w wieku powyżej 60 lat, tymczasem Organizacja Narodów Zjednoczonych (ONZ) jako początek starości ustaliło wiek 65 lat [1]. Zjawisko starzenia się społeczeństwa jest procesem dotyczącym nie tylko Polski, lecz całej Europy. Z każdym rokiem w Polsce zwiększa się udział osób starszych w strukturze demograficznej społeczeństwa, natomiast zmniejsza się liczba osób młodych. Według opracowanej przez Główny Urząd Statystyczny „Prognozy ludności na lata 2014 – 2050", w 2050 roku odsetek ludzi starszych w Polsce może wynieść nawet 35% ogółu populacji [2].

Proces starzenia się organizmu człowieka prowadzi do licznych zmian w funkcjonowaniu jego narządów i układów. Podstawowa przemiana materii i aktywność fizyczna seniorów zazwyczaj ulega wyraźnemu zmniejszeniu. Zachodzą zmiany w składzie ciała. Beztłuszczowa masa ciała zmniejsza się na rzecz tkanki tłuszczowej. W związku z powyższym, zapotrzebowanie na energię u osób w wieku podeszłym maleje [3]. Największą konieczność modyfikacji sposobu żywienia powodują procesy starzenia zachodzące w układzie pokarmowym. Należą do nich: spadek wydzielania soków żołądkowych, hormonów i aktywności enzymów trawiennych, pogorszenie jakości błony śluzowej przewodu pokarmowego, zmniejszenie wchłaniania w jelitach. Trzustka u osób starszych wydziela mniejsze ilości insuliny, przez co węglowodany są gorzej tolerowane [4]. Starzenie się organizmu prowadzi również do zmian w odczuwaniu smaku i zapachu. Wraz z wiekiem zmniejsza się zdolność organizmu do przekształcania witaminy D w jej aktywne formy [3]. Pogorszenie procesów transformacji witaminy D oraz zawartości wapnia w organizmie bezpośrednio wiąże się ze związanym z wiekiem spadkiem masy tkanki kostnej. Zmniejszeniu ulega również masa tkanki mięśniowej [4]. Ze względu na wyżej wymienione zmiany zachodzące w starzejącym się organizmie oraz choroby towarzyszące starości, dieta osób w wieku podeszłym

powinna być odpowiednio zbilansowana. Zastosowanie profilaktyki żywieniowej i dostosowanej do możliwości seniora aktywności fizycznej, daje osobom starszym szansę na dłuższe życie w zdrowiu i ogólnej sprawności. Dieta powinna być dostosowana zarówno do wieku, jak i stanu zdrowia danej osoby.

Celem niniejszej pracy jest przegląd zaleceń z zakresu żywienia w wybranych chorobach wieku podeszłego.

ŻYWIENIE W CHOROBIE ALZHEIMERA

Najnowsze badania wykazują, iż hiperinsulinemia dodatnio koreluje z postępem choroby Alzheimera. Udowodniono, że mózg osoby chorej na tę chorobę wykazuje wadliwą sygnalizację oraz zmniejszoną wrażliwość na insulinę, której działanie istotne jest dla przeżycia neuronów i prawidłowego funkcjonowania mózgu [5, 6]. Obecnie uważa się, że insulina poprawia pamięć oraz zdolności poznawcze u pacjentów z chorobą Alzheimera [7, 8]. Wykazano, że może mieć ważne implikacje terapeutyczne, szczególnie w początkowej fazie tej choroby [9, 10]. Nowe metody leczenia w odniesieniu do choroby Alzheimera wynikają z działań zmierzających do odkrycie mechanizmów stanowiących tzw. insulinooporność mózgu [5].

Żywienie pacjentów z chorobą Alzheimera nie powinno znacząco odbiegać od zasad żywienia przyjętych dla zdrowych osób w starszym wieku. Jednak w przebiegu choroby bardzo często obserwuje się niedożywienie, które występuje aż u 25% osób [11]. Niedożywienie pogłębia otępienie, przyczynia się do większej zapadalności na inne choroby, zwiększa ryzyko zgonu. Zmiany zachodzące w mózgu w wyniku choroby mogą spowodować zaburzenia w spożywaniu żywności i napojów. Należy, więc regularnie sprawdzać stan odżywienia u tych pacjentów. W przypadku stwierdzenia niedożywienia należy wprowadzić leczenie żywieniowe. Polskie Towarzystwo Neurologiczne zaleca, aby u osób z chorobą Alzheimera, u których występują łagodne zaburzenia odżywiania wdrożyć doustną suplementację makroskładników żywieniowych (ONS – *oral nutritional suplementation*). Jej stosowanie poprawia stan odżywienia i zmniejsza ryzyko śmiertelności wśród niedożywionych pacjentów [12].

Ważnym wsparciem dla farmakoterapii osób z chorobą Alzheimera stanowią doustne, specjalistycznych środki odżywcze, które przyczyniają się do korzystnych zmian w zakresie neuroprzekaźnictwa (nutraceutyków), co z kolei wpływa na kondycję poznawczą pacjentów [13]. W Polsce jedynym takim preparatem o udokumentowanym, korzystnym działaniu u osób z deficytami funkcji poznawczych jest Souvenaid® [12, 14]. Stanowi on kombinację odpowiednio wyselekcjonowanych składników odżywczych. Zawiera w swoim składzie: DHA (kwas dokozaheksaenowy), EPA (kwas eikozapentaenowy), monofosforan urydyny, cholinę, kwas foliowy, witaminy B6, B12, E, C, selen oraz fosfolipidy, w takiej ilości, w jakiej nie są możliwe do uzyskania w ramach zrównoważonej diety [13, 15]. Z licznych badań klinicznych wynika, że diety przemysłowe, składające się z wyżej wymienionych składników odżywczych mogą wspomagać neuroplastyczność mózgu poprzez tworzenie nowych połączeń synaptycznych [16].

W przebiegu choroby Alzheimera mogą pojawić się zaburzenia połykania. Ich najczęstszą formą jest przetrzymywanie pokarmu w ustach. W niektórych przypadkach występuje zbyt szybkie jedzenie, które prowadzi do zakrztuszeń. Może dojść też do próby konsumpcji towarów nieprzeznaczonych do spożycia. W przypadku zaburzeń połykania stosuje się odpowiednią pozycję podczas jedzenia, a żywność poddaje się miksowaniu lub zagęszczaniu. Korzystnie może działać większa ilość przypraw [12].

Ważnym aspektem w odżywianiu osób cierpiących na chorobę Alzheimera jest odpowiednie przygotowywanie potraw oraz warunki ułatwiające spożywanie pokarmów. Wraz z postępem choroby często dochodzi do gorszego odczuwania smaków, najczęściej najlepiej poznawanym smakiem jest smak słodki. W związku z tym korzystne jest odpowiednie przyprawianie potraw, w tym celu przydatne są produkty spożywcze o naturalnie słodkim smaku, np. marchewka. Aby zapewnić jak najwyższy komfort spożywania posiłków, istotne jest stosowanie odpowiedniej zastawy stołowej upraszczającej jedzenie [12]. Sztućce powinny mieć grube uchwyty. Korzystnym jest stosowanie talerzy, które nie zlewają się z kolorem obrusu oraz jedzenia. W przypadku, gdy senior bardzo szybko zapomina o tym, że jadł, dopuszcza się konsumowanie niewielkich przekąsek w postaci pokrojonych warzyw i owoców albo czekolady. Trzeba jednak kontrolować ich ilość [11].

Dieta śródziemnomorska, bogata w ryby, świeże owoce i warzywa, jest zalecana jako element profilaktyki choroby Alzheimera oraz wielu innych schorzeń, ze względu na wysoką zawartość przeciwutleniaczy i kwasów omega-3 [11]. Badania wykazały, że staranne przestrzeganie zasad diety śródziemnomorskiej w połączeniu z aktywnością fizyczną może obniżyć ryzyko choroby Alzheimera nawet o 40% [17] .

Największe znaczenie w prewencji choroby Alzheimera mają kwasy tłuszczowe omega-3, które wykazują działanie przeciwagregacyjne, przeciwzapalne oraz przeciwzakrzepowe. Kwasy tłuszczowe omega-3 korzystnie wpływają na zdolności neuroprzekaźnictwa, a także na pobudliwość błon neuronów [18]. Obecność tłustych ryb w jadłospisie, będących głównym źródłem omega-3, spożywanych co najmniej dwukrotnie w ciągu tygodnia, może obniżyć ryzyko choroby Alzheimera aż o 60% [11].

Przeciwutleniacze, zwłaszcza witaminy A, C i E, również skutecznie zapobiegają chorobie Alzheimera. Witaminy te uczestniczą w przeciwdziałaniu wolnym rodnikom, które przyczyniają się do powstawania stresu oksydacyjnego będącego jednym z czynników sprzyjających powstawaniu tej choroby [19]. W badaniach wykazano, że stężenie witamin E oraz C w osoczu osób chorych kształtowało się na niższym poziomie, niż u osób zdrowych. Dostarczanie do organizmu odpowiednich ilości tych witamin może zapobiegać chorobie Alzheimera [20].

Flawonoidy odgrywają ważną rolę w prewencji choroby Alzheimera [11]. Usuwają wolne rodniki oraz redukują ich

powstawanie, działają ochronnie na witaminy antyoksydacyjne w procesach oksydacyjnych, a także przyczyniają się do wstrzymywania peroksydacji lipidów oraz zwiększania stabilności błon komórkowych. Korzystne działanie flawonoidów na zachowanie funkcji poznawczych potwierdzone zostało w wielu badaniach [20]. Najwięcej flawonoidów znajduje się w gorzkiej czekoladzie (posiadającej w składzie minimum 70% kakao), można je też znaleźć w owocach takich jak: aronia, jagody, czarne porzeczki, winogrona, truskawki i wiśnie. Znajdują się także w warzywach m. in. kapuście, brokułach, pomidorach, sałacie, papryce, nasionach roślin strączkowych, zbożach, kawie, herbacie i w czerwonym winie [11].

Witamina D wpływa pozytywnie na zachowanie funkcji poznawczych. Osoby z wyższym poziomem tej witaminy charakteryzują się lepszymi rezultatami uzyskiwanymi w testach funkcji poznawczych, a także mniejszym prawdopodobieństwem zachorowania na schorzenia otępienne [21]. Witamina D wspiera makrofagi w pochłanianiu beta-amyloidu, na drodze fagocytozy. Wykazuje również działanie ochronne na neurony.

Znajdująca się w kurkumie kurkumina, działa korzystnie w profilaktyce choroby Alzheimera. Charakteryzuje się silnymi właściwościami antyoksydacyjnymi i przeciwzapalnymi. W mózgu prowadzi do mniejszego odkładania się złogów beta – amyloidu [11].

Ważnym jest też dostarczanie wraz z dietą do organizmu odpowiednich ilości witamin z grupy B. Witaminy te, w szczególności B_6, B_{12} oraz kwas foliowy wpływają na metabolizm homocysteiny, która powstaje w procesie przekształcania metioniny do cysteiny [17]. Niedobór tych witamin przyczynia się do zwiększonego stężenia homocysteiny we krwi [22]. Zbyt duża ilość produktów spożywczych pochodzenia zwierzęcego prowadzi do zwiększonego stężenia homocysteiny, której podwyższony poziom może przyspieszać powstawanie złogów beta-amyloidu w układzie nerwowym oraz przyczyniać się do postępu choroby Alzheimera [11, 22].

Zdrowy styl życia, utrzymanie prawidłowej masy ciała, odpowiednia dieta oraz dostosowana do możliwości aktywność fizyczna stanowią istotną rolę w prewencji choroby Alzheimera [22].

ŻYWIENIE W CHOROBIE PARKINSONA

We wczesnych okresach rozwoju choroby Parkinsona dieta powinna opierać się na zasadach żywienia dla seniorów. Zalecana ilość kalorii to 25 – 30 na każdy kilogram prawidłowej masy ciała. W przypadku występowania zaburzeń ruchowych dochodzi do zwiększonego wydatku energetycznego. W związku z tym ilość kalorii w planowanej diecie należy zwiększyć, zazwyczaj do 30 – 35 kcal na kilogram należnej masy ciała [23, 24]. W chorobie Parkinsona, ze względu na uporczywe objawy choroby, a także przyjmowane leki, często dochodzi do pojawienia się niedożywienia. Stan odżywienia u osób z tą chorobą winno się kontrolować minimum raz do roku [24].

Najczęściej stosowanym lekiem w chorobie Parkinsona są preparaty lewodopy. Terapia ta wymaga zmian w podawaniu białka, ponieważ aminokwasy ograniczają wchłanianie lewodopy. Zaleca się, aby białko spożywane było w ilości około 0,8 g/kg masy ciała. Pacjenci powinni zażywać lek pół godziny przed posiłkiem albo 2 godziny po nim. U osób leczonych lewodopą, białko można podawać na dwa sposoby, w zależności od zaawansowania choroby oraz stylu życia chorego. Pierwszą modyfikacją jest stosowanie diety z dystrybucją białka. Jest ona proponowana dla osób w mało zaawansowanym stadium choroby oraz będących aktywnymi w późnych godzinach. Ilość spożywanego białka jest proporcjonalnie rozdzielona pomiędzy poszczególne posiłki. Istotne jest zachowanie odpowiedniego stosunku pomiędzy białkiem i węglowodanami, ponieważ dzięki temu nie zostają zachwiane optymalne warunki do wchłaniania lewodopy. Prawidłowa proporcja białka i węglowodanów powinna kształtować się na poziomie 1:5 bądź 1:6.

Drugim rodzajem diety stosowanej podczas zażywania lewodopy jest dieta z redystrybucją białek. Ta modyfikacja zalecana jest zazwyczaj osobom na bardziej zaawansowanym etapie choroby, których szczyt aktywności przypada na godziny poranne. Pokarmy zawierające duże ilości białka w większości spożywa się wieczorem. W posiłkach wieczornych powinny znaleźć się produkty bogate w białko, takie jak: ryby, mięsa, produkty mleczne, zboża. We wcześniejszych godzinach należy spożywać maksymalnie 10% dobowej dawki białka. Podstawę tych posiłków powinny stanowić produkty z małą zawartością białka, głównie owoce, warzywa, a także tłuszcze. Dzięki tym zmianom lewodopa działa skuteczniej [25] .

W żywieniu osób z chorobą Parkinsona należy zwracać uwagę na odpowiednią podaż witamin. Niski poziom witaminy D może być czynnikiem przyczyniającym się do rozwoju choroby Parkinsona [24, 26]. Witamina ta działa korzystnie w przypadku spadku masy kostnej, który również występuje się w przebiegu choroby Parkinsona. Ważne jest spożywanie odpowiednich ilości kwasu foliowego, witamin B12, C, E oraz koenzymu Q10 [24].

Bardzo częstym objawem w chorobie Parkinsona (występującym w prawie 85% przypadków) są zaparcia. Do ich powstawania przyczyniają się zmiany zachodzące w układzie nerwowym, przewodzie pokarmowym oraz przyjmowane leki. Pomocne w leczeniu zaparć jest stosowanie błonnika w ilości 25 g/dobę oraz płynów w ilości ponad 2 litry. Przydatne są także produkty spożywcze poddawane procesowi fermentacji, np. jogurty, kefiry, owoce suszone, miód, oliwa z oliwek oraz produkty z pełnego ziarna [25].

Zaburzenia połykania, które mogą dotyczyć 80% chorych, niosą za sobą konieczność zmiany konsystencji żywności oraz sposobu podawania posiłków [24].

ŻYWIENIE W OSTEOPOROZIE

Żywienie w osteoporozie powinno być skoncentrowane na dostarczeniu odpowiednich ilości składników, takich jak: wapń, witamina D, fosfor, magnez, witamina K oraz fitoestrogeny. W związku z powyższym, istotne jest spożywanie produktów mlecznych, ryb, warzyw zaliczanych

do kapustnych oraz sezamu. Są to produkty zawierające w swoim składzie znaczne ilości wapnia [27].

Witamina D dostarczana jest z pożywieniem między innymi z rybami, mlekiem, czy tranem, a także wytwarzana pod wpływem promieni słonecznych. Zazwyczaj źródła te nie pokrywają zapotrzebowania organizmu na tę witaminę. Ważnym jest więc jej suplementowanie [28].

Fosfor jest składnikiem obficie występującym w jedzeniu np. w produktach mięsnych, zbożowych oraz mlecznych. Są one często spożywane, dlatego rzadko zdarzają się jego niedobory. Należy jednak zwrócić uwagę na zachowanie odpowiedniej proporcji między nim, a wapniem, która najlepiej powinna być równa 1:1 [28].

Witamina K uczestniczy w mineralizowaniu kości. Pełni ważną funkcję w leczeniu osteoporozy. Występuje w takich produktach spożywczych jak: liściaste warzywa, pomidory czy wątróbka [28].

W osteoporozie pomenopauzalnej istotnym składnikiem pożywienia stają się fitoestrogeny, ponieważ naśladują one prawdziwe estrogeny. Działają zagęszczająco na tkankę kostną. Można je znaleźć między innymi w soi [29].

ŻYWIENIE W MIAŻDŻYCY

Podstawowym elementem żywienia w miażdżycy jest redukcja masy ciała, w przypadku osób z nadwaga lub otyłością. Dieta odchudzająca powinna być indywidualnie dopasowana do potrzeb organizmu każdego pacjenta [23].

Według zaleceń WHO zawartość tłuszczu w diecie osób z miażdżycą powinna wahać się w granicach od 15 do 30% wartości energetycznej diety, przy czym zawartość poszczególnych rodzajów kwasów tłuszczowych omega winna kształtować się następująco: kwasy tłuszczowe omega 6 od 5 do 8%, zaś kwasy tłuszczowe omega 3 od 1 do 2%. Cholesterol nie powinien przekraczać ilości 300 mg w ciągu dnia [23].

Podczas dokonywania wyborów żywieniowych konieczne jest zwrócenie uwagi na produkty spożywcze nie obfitujące w tłuszcze nasycone. Należy wybierać chude gatunki mięs, takie jak kurczak lub indyk. Mleko i jego przetwory nie powinny być pełnotłuste. Ważnym jest, aby dwa razy w tygodniu były spożywane ryby. Ze względu na wysoką zawartość cholesterolu zalecane jest ograniczone spożycie żółtek jaj oraz podrobów. W celu dostarczenia odpowiednich ilości włókna pokarmowego należy wybierać zbożowe produkty pełnoziarniste, jak również spożywać znaczne ilości warzyw oraz owoców [23].

ŻYWIENIE PO UDARZE MÓZGU

Główną przyczyną zmiany sposobu odżywiania u wielu osób po przebytym udarze jest występowanie zaburzeń połykania, które zwiększają możliwość niedożywienia. W zależności od stanu pacjenta konieczne jest wprowadzenie odpowiednich modyfikacji żywienia. Pacjenci po udarze mózgu mają zazwyczaj wyższe zapotrzebowanie na energię ze względu na występowanie dolegliwości poudarowych, takich jak: ból, pobudzenie oraz większy wysiłek towarzyszący realizowaniu wszystkich czynności [23].

Występowanie dysfagii niesie za sobą ryzyko pojawienia się niedożywienia, odwodnienia, zachłyśnięcia oraz zachłystowego zapalenia płuc, które obarczone jest dużym ryzykiem śmierci [30]. Sposób żywienia należy dostosować do stopnia nasilenia zaburzeń połykania. W przypadku minimalnej dysfagii nie występuje potrzeba zmian żywieniowych. Wraz z większym zaawansowaniem zaburzenia zachodzi jednak konieczność wprowadzania coraz większych modyfikacji, począwszy od wdrażania specjalnych technik połykania i zmiany konsystencji diety, aż po zaprzestanie odżywiania drogą doustną. Żywienie należy zmodyfikować tak, aby możliwość zachłyśnięcia była jak najmniejsza, a równocześnie została zapewniona realizacja potrzeb żywieniowych [31].

W żywieniu osób z dysfagią istotne jest wybieranie produktów spożywczych o konsystencji niepowodującej problemów przy przełykaniu. Chorzy z małymi zaburzeniami połykania, u których występuje niskie prawdopodobieństwo zachłyśnięcia, mogą przyjmować potrawy o konsystencji stałej, jednak możliwej do rozdrobnienia przy pomocy języka. Wymogi te spełniają między innymi: pieczywo podawane bez skórki, warzywa ugotowane do miękkości, tarte warzywa i owoce, sałatki z miękkich warzyw, mięso najlepiej w postaci zmielonej z sosem, potrawy z jaj, przetwory mleczne w łatwej do połknięcia formie, np. jogurt. Powinno się wykluczyć z diety potrawy mogące powodować podrażnienie. Do takich produktów zalicza się dania mające konsystencję sypką, chrupiącą, twardą, ciągnącą, np. sypkie kasze, produkty pełnoziarniste, suche gatunki mięs, jak również cytrusy [30].

W przypadku występowania umiarkowanych zaburzeń połykania i możliwości zachłyśnięcia na średnim poziomie rekomendowane są potrawy podawane pod postacią papek. Wszystkie potrawy powinny być pozbawione wyraźnych kawałków. Dania zalecane w tym stopniu dysfagii to: pszenne pieczywo z dodatkiem gładkich past, zupy w postaci kremów, rozgotowane kasze, dobrze ugotowane warzywa, puree ziemniaczane, mięso z sosem, najlepiej podawane w formie puree, gotowane lub przetarte owoce pozbawione pestek i skóry, przetwory mleczne o gładkiej konsystencji. Dodatkowo przeciwwskazane jest łykowate mięso oraz warzywa, a także sałatki [30].

Osoby z ciężką dysfagią oraz dużą możliwością zachłyśnięcia powinny spożywać produkty przecierane, półpłynne lub zmieniające się w takie w ustach. Wszystkie spożywane potrawy, takie jak: zupy, warzywa, owoce, przetwory mleczne muszą charakteryzować się gładką konsystencją, aby zminimalizować ryzyko zachłyśnięcia [30].

Osoby po udarze mózgu, będące w stanie śpiączki oraz pacjenci z bardzo ciężką dysfagią powinni być karmieni pozajelitowo przy pomocy zgłębnika nosowo–żołądkowego lub gastrostomii, z wykorzystaniem diety o konsystencji płynnej. Przydatne są też diety przemysłowe [23].

W celu redukcji bardzo częstego powikłania zaburzeń połykania, jakim jest niedożywienie, konieczne jest przeprowadzanie oceny stanu odżywienia u chorych, kontroli masy ciała oraz jakości i ilości przyjmowanych potraw oraz płynów. W razie konieczności, należy jak najwcześniej rozpocząć prowadzenia leczenia żywieniowego [32].

Tabela I. Produkty zalecane i przeciwwskazane w diecie DASH.

Produkty zalecane w diecie DASH	Produkty ograniczone w diecie DASH
Warzywa	Sól kuchenna
Owoce	Słodycze oraz słodkie napoje
Zbożowe produkty pełnoziarniste	Mięso czerwone i produkty mięsne
Mleko i jego przetwory z niską zawartością tłuszczu	
Rośliny strączkowe	
Drób	
Ryby	
Orzechy	

Tabela II. Składniki występujące w diecie DASH w dużych i małych ilościach

Składniki występujące w dużych ilościach	Składniki występujące w małych ilościach
Wapń	Kwasy tłuszczowe nasycone
Magnez	Izomery trans kwasów tłuszczowych
Potas	Cholesterol
Błonnik	Sód

Istnieje kilka sposobów na ułatwienie osobom chorym przyjmowania posiłków. Jednym z nich jest przyjmowanie przez pacjenta podczas jedzenia odpowiedniej pozycji. Powinno się, o ile jest to możliwe, spożywać posiłki na siedząco z prostą szyją i głową skierowaną przed siebie. W przypadku, gdy pacjent jest karmiony przez inną osobę, jedzenie winno znajdować się w obrębie jego wzroku. Wpływa to korzystnie na przełykanie, a także zwiększa ochotę na pokarm. Osoba odpowiedzialna za karmienie powinna modyfikować ilość podawanego jednorazowo pokarmu oraz szybkość jego podawania zgodnie z potrzebami pacjenta. Kolejnym sposobem usprawniającym spożywanie pokarmów są specjalne ćwiczenia połykania prowadzone z terapeutą, dzięki którym minimalizuje się ryzyko zachłyśnięcia. Ćwiczenia te noszą nazwę połykania nagłośniowego oraz manewru Mendelsohna [31].

Spożywanie płynów może stanowić poważny problem u osób z dysfagią, ponieważ bardzo często powodują zachłyśnięcie. W celu ułatwienia picia płynów korzystne jest ich zagęszczanie. Dostępne są środki zagęszczające, występujące pod postacią proszku, które w łatwy sposób pozwalają na zmianę konsystencji płynów na gęściejszą [31]. Dobrym sposobem jest również stosowanie słomek do napojów oraz kubków z nisko znajdującym się dziubkiem [31].

ŻYWIENIE W NADCIŚNIENIU TĘTNICZYM

Dla osób z nadciśnieniem tętniczym zaleca się dietę DASH. Przynosi ona korzyści w postaci obniżenia ciśnienia tętniczego, jest przydatna w zapobieganiu chorobom układu krążenia i cukrzyca typu 2. Minimalizuje też prawdopodobieństwo śmierci na skutek wyżej wymienionych schorzeń. Charakteryzuje się ona zwiększoną ilością produktów korzystnie wpływających na zdrowie oraz małą ilością tych, które działają negatywnie na nasz organizm. Produkty zalecane i ograniczane w diecie DASH przedstawiono w tabeli I i II [33].

Dla osób ze zbyt wysokimi wartościami ciśnienia tętniczego bardzo ważnym elementem terapii jest aktywność fizyczna. Najlepszą jej formą jest trening aerobowy o umiarkowanej intensywności. Zaleca się pływanie, jazdę na rowerze, długie spacery oraz bieganie trwające 30 minut z częstotliwością od 3 do 7 razy w tygodniu [34].

ŻYWIENIE W CUKRZYCY TYPU 2

Prawidłowo zbilansowana dieta jest niezwykle ważna w leczeniu chorych na cukrzycę typu 2. Dzięki odpowiedniemu odżywianiu możliwe jest poprawienie jakości życia i stanu zdrowia osób cierpiących na tę chorobę. Właściwe żywienie przyczynia się również do zapobiegania powikłaniom cukrzycy. Działania dietetyczne prowadzone u osób cierpiących na cukrzycę mają na celu utrzymanie prawidłowego poziomu glukozy I lipoprotein we krwi, uzyskanie masy ciała na optymalnym poziomie oraz kontrolę ciśnienia tętniczego. W terapii cukrzycy bardzo istotne jest, aby osoby chore spożywały posiłki w regularnych odstępach czasowych, a ilość węglowodanów była rozplanowana równomiernie pomiędzy poszczególne posiłki [35].

Ilość kalorii w diecie osób chorujących na cukrzycę powinna być dostosowana do zapotrzebowania organizmu. U chorych, u których zachodzi konieczność zredukowania masy ciała, powinno się zastosować ograniczenie kaloryczne [36].

Ilość węglowodanów zawartych w diecie osób z cukrzycą zgodnie z zaleceniami Polskiego Towarzystwa Diabetologicznego powinna stanowić 45% kalorii. Węglowodany w diecie osób z cukrzycą powinny pochodzić z produktów cechujących się dużą zawartością błonnika i z indeksem glikemicznym nie przekraczającym 55. Takimi produk-

Tabela III. Udział kwasów tłuszczowych w diecie

Rodzaje kwasów tłuszczowych	Maksymalny udział w diecie
Kwasy tłuszczowe nasycone	Maksymalnie 10%
Kwasy tłuszczowe jednonienasycone	Maksymalnie 20%
Kwasy tłuszczowe wielonienasycone	Od 6 do 10%

tami są między innymi warzywa oraz produkty zbożowe z pełnego ziarna. Jeśli węglowodany znajdujące się w diecie mają wyżej wymienione cechy, to ich ilość może być zwiększona nawet do 60% ogółu przyjmowanej energii, jednak jest ona zalecana osobom obciążonym dużym wysiłkiem fizycznym [35]. Konieczne jest maksymalne ograniczenie ilości spożywanych cukrów prostych. Mleko oraz owoce zwierają duże ilości cukrów, dlatego powinny być spożywane w ograniczonych ilościach. Niezbędne jest wyeliminowanie z diety słodyczy i soków owocowych [36].

Białko u osób chorujących na cukrzycę w większości przypadków powinno być przyjmowane zgodnie z zaleceniami dla osób zdrowych i stanowić od 15 do 20% energii. Wyjątek stanowią osoby z cukrzycą typu 2 i towarzyszącą nadmierną masą ciała jeśli nie występują u nich zaburzenia ze strony nerek, w takim przypadku podaż białka może ulec zwiększeniu do nawet 30% ogólnej ilości energii [35].

Ilość tłuszczu w diecie osób z cukrzycą powinna mieścić się w granicach od 25 do 40%. Niezwykle istotną kwestią jest właściwy stosunek kwasów tłuszczowych. Odpowiedni udział kwasów tłuszczowych w diecie przedstawiono w tabeli III. Tłuszcz powinien pochodzić produktów roślinnych oraz tłustych ryb [35].

Prawidłowe spożycie błonnika jest bardzo ważne w leczeniu dietetycznym cukrzycy. Błonnik pokarmowy wywiera wpływ na zmniejszanie glikemii poposiłkowej poprzez działanie opóźniające tempo opróżniania się żołądka, jak również trawienia i wchłaniania składników odżywczych. Takie działanie mają zwłaszcza jego rozpuszczalne frakcje. Rekomendowane jest spożycie błonnika pokarmowego na poziomie 25 do 50 g dziennie lub w ilości 15 do 25 g przypadającej na każde 1000 kalorii [36].

Alkohol nie należy do produktów zalecanych w diecie osób cierpiących na cukrzycę, ponieważ może zwiększać ryzyko hipoglikemii. Maksymalna ilość czystego alkoholu przyjmowana przez osoby z cukrzycą nie powinna przekraczać 20 g dla kobiet i 30 g dla mężczyzn, przy czym nie należy konsumować napojów alkoholowych bez uprzedniego spożycia posiłku [36]. Sól kuchenna może być spożywana w ilościach zalecanych dla osób zdrowych, czyli w ilości 5 g na dobę [35].

ŻYWIENIE W STWARDNIENIU ZANIKOWYM BOCZNYM

Zasady żywienia u osób ze stwardnieniem zanikowym bocznym zależą od zaawansowania choroby. U ludzi z tym schorzeniem występuje wyższe zapotrzebowanie energetyczne, ze względu na intensywny wysiłek towarzyszący chorobie [37].

Jeśli pojawi się dysfagia, konieczna jest modyfikacja konsystencji posiłków, tak aby ich połykanie w jak najmniejszym stopniu groziło zachłyśnięciem. Zalecane są produkty spożywcze o gładkiej strukturze, niewymagające gryzienia, najlepiej w postaci papki. Produkty płynne należy zagęszczać, aby zminimalizować możliwość zachłyśnięcia [30].

W przypadku stwierdzenia obniżenia masy ciała powyżej 10% zalecane jest wprowadzenie odżywiania poprzez przezskórną gastrostomię endoskopową (PEG). Umożliwia ona podawanie pokarmu prosto do żołądka [37]. Dzięki zastosowaniu PEG organizm zostaje zaopatrzony w odpowiednią ilość składników odżywczych. Żywienie przez PEG powinno się rozpocząć zanim wydolność płuc obniży się poniżej 50%, ponieważ wtedy zabieg nie niesie ze sobą dużego ryzyka. W przypadku braku możliwości wykonania PEG konieczne jest wprowadzenie żywienia pozajelitowego [38]. Poprzez PEG powinno się podawać diety przemysłowe. Dopuszczalne jest również stosowanie normalnej diety jednak w formie dokładnie rozdrobnionej. Podawanie jej grozi jednak niedostateczną podażą składników pokarmowych, ze względu na brak możliwości dokładnego oszacowania ich zawartości. Istnieje kilka sposobów podawania pokarmu poprzez gastrostomię. Pierwszy ze sposobów to metoda bolusa, w tym przypadku pożywienie jest podawane przy pomocy strzykawki, ewentualnie pompy. W niedługim czasie wprowadza się dużą ilość żywności, jednak pomiędzy następnymi dawkami są zachowane odpowiednie przerwy. Drugim sposobem jest metoda wlewu ciągłego. W tej metodzie pokarm wprowadza się wolno przy użyciu pompy, a podawanie trwa nawet kilka godzin. Trzecim sposobem jest metoda grawitacyjna. Pożywienie dostaje się do żołądka dzięki działaniu grawitacji [39].

PODSUMOWANIE

Ważne jest, aby dieta osób starszych dostarczała odpowiednich ilości składników odżywczych, była dostosowana do występujących u nich chorób oraz dolegliwości, związanych z procesem starzenia, a równocześnie w miarę możliwości była zgodna z upodobaniami seniora.

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REVIEW ARTICLE
PRACA POGLĄDOWA

ANALYSIS OF REGULAR DENTAL CHECKUPS OF KYIVITES IN STOMATOLOGICAL ESTABLISHMENTS OF VARIOUS PROPERTY FORMS

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ABSTRACT

The aim: carry out analysis of regular dental checkups in Kyiv in state and private dental establishments.

Materials and methods: The analysis was conducted using the statistical reports (approved standard №20) which have been obtained in Kyiv and Ukraine from 2008 till 2017. The method of copying data with using statistical estimation methods was applied.

Results: The authors have established significant dental preventive measures decline in Kyiv state dental establishments from 2008 till 2017. A tendency toward increased private dental sector within the dental prevention has been noted.

Conclusions: The obtained results will be used to substantiate concepts of municipal stomatological dental care improvement as well as to introduce the university clinic model.

KEY WORDS: regular dental checkups, population of Kyiv, state and private stomatological establishments

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INTRODUCTION

Oral health is essential to general health and well-being and greatly influences quality of life [1]. Stomatological diseases are important components of noncommunicable diseases, which continue to be a leading public health problem in the WHO European Region [2,3,4].

Considerable incidence of stomatological diseases among Ukrainians makes the issue of preserving and improving stomatological health medically and socially valuable [5,6,7,8,9].

This is why the main direction of the stomatological service functioning should be application of its preventive strategy, aimed at preserving stomatological health status of the population. The main ways of preventive strategy application are hygienic education, regular checkups and stomatological preventive treatment [1,10,11,12].

Management of stomatological service and substantiation of its improvement, including preventive measures, is impossible without systematic generalization and analysis of the medical statistical reports on its functioning [8,9].

THE AIM

The aim: carry out analysis of regular dental checkups in Kyiv in state and private dental establishments.

MATERIALS AND METHODS

Analysis of regular dental checkups was conducted on the base of the statistical reports (№ 20), which have been obtained in Kyiv and Ukraine from 2008 till 2017. The assessment included data obtained in the state and private institutions, from adult and pediatric dental patients. The method of copying data with using statistical estimation methods was applied.

REVIEW AND DISCUSSION

The analysis of Kyiv state and municipal preventive service shows significant decline in preventive service volume during last decade, especially regarding the adult Kyivites.

In 2017, during regular checkups, 660621 adult patients were examined in municipal and state stomatological establishments of Kyiv, which represents less than one third (28%) of all Kyivites older than 18 years (17.2% of all Ukrainians). Compared to 2008, the relative share of those who were examined during regular checkups decreased by 16% in Kyiv and 4.9% in Ukraine (see.tab.1).

The relative share of the patients who were examined within the regular checkups made up less than a half (45-46%) in Kyiv, and one fourth (23-24%) in Ukraine from all adults who referred for stomatological service.

Among all adults examined within the regular checkups schedule in 2017, 82.1% required dental treatment in Kyiv, and 55.6 % in Ukraine. These data showing dental treatment demands haven't changed since 2008, when they made up 81.2% and 56.3%, respectively.

In 2017 in Kyiv relative share of patients who received treatment after regular checkups was 71.9%, i.e., almost

Table 1. Regular dental checkups of adults in municipal and state stomatological establishments, Kyiv, Ukraine, 2008, 2012, 2017 (own development according to the data of statistical reports)

Region/years	2008	2012	2017	Absolute increase 2017/2008
Relative share of adults examined within the checkup schedule (%)				
Kyiv	44.0	35.0	28.0	-16.0
Ukraine	22.1	21.3	17.2	-4.9
Relative share of all adults examined on their own referral (y %)				
Kyiv	45.6	46.0	45.5	-0.1
Ukraine	23.3	23.7	23.6	0.3
The adults who after checkups required dental treatment (% from all examined adults)				
Kyiv	81.2	81.4	82.1	0.9
Ukraine	56.3	55.4	55.6	-0.7
Relative share of those adults who after checkups required treatment and received it				
Kyiv	73.4	75.5	71.9	-1.4
Ukraine	77.1	77.6	74.7	-2.4
Relative share of those who were treated after regular checkups and upon their own referral (%)				
Kyiv	44.0	21.5	16.5	-27.5
Ukraine	22.1	23.6	18.7	-3.4

Table 2. Regular dental checkups of children in state and municipal stomatological establishments in Kyiv, Ukraine, 2008,2012, 2017 (own development according to the data of statistical reports)

Region/ years	2008	2012	2017	Absolute increase 2017/2008
Relative share of those children examined within regular checkups (y %)				
Kyiv	113.7	105.7	90.8	-22.9
Ukraine	70.9	69.5	56.4	-14.5
Relative share of children undergoing checkups related to those who referred for stomatological service (%)				
Kyiv	49.4	49.7	51.6	2.2
Ukraine	42.7	42.4	42.3	-0.4
Relative share of the children who underwent checkups and required dental treatment (% from the amount of examined children)				
Kyiv	59.0	54.6	59.1	0.1
Ukraine	49.6	48.8	48.7	-0.9
Relative share of the children who received treatment during the checkups related to the children who required treatment (%)				
Kyiv	73.5	71.9	68.0	-5.5
Ukraine	83.3	82	78.5	-4.8
Relative share of those who received dental treatment during checkups and upon their own referral (%)				
Kyiv	113.7	41.5	36.8	-76.9
Ukraine	70.9	41.9	33.8	-37.1

one third of the examined patients (28.1%), who required dental treatment, hadn't received it before. Relative share of the patients who received dental treatment during regular checkups related to total number of adults who required it, being lower in Kyiv than in Ukraine, throughout all study period, and it tended to decline.

The relative share of those adult patients who received dental treatment during regular checkups and after their own referrals showed that in 2017 the share of such patients in Kyiv was only 16.5% of all adults in Kyiv, and 18.7% of all Ukrainians. Compared to 2008, these characteristics decreased in Kyiv by 27.5% and in Ukraine – by 3.4%.

So, the cause of unsatisfactory stomatological health status of the adults is insufficient prophylaxis during both primary and secondary stomatological prevention, which is evidenced by negative dynamic pattern of regular prevention among adults in both municipal and state establishments of Kyiv and Ukraine.

The adult stomatological health is predisposed for children behavioral patterns [13,14], so conducting stomato-

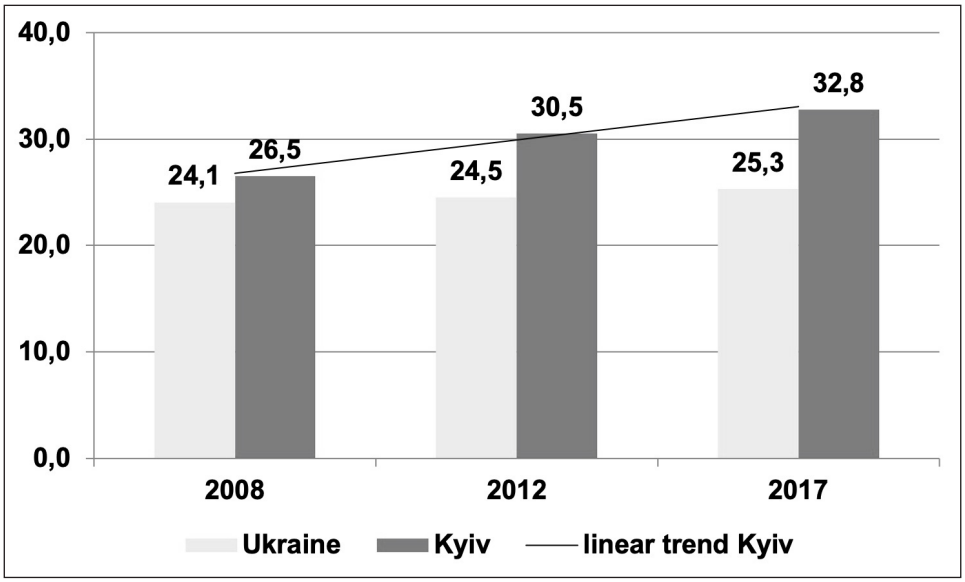

Fig.1. Relative share of complicated caries among adults, Kyiv, Ukraine 2008, 2012, 2017 (%)(own development according to the data of statistical reports)

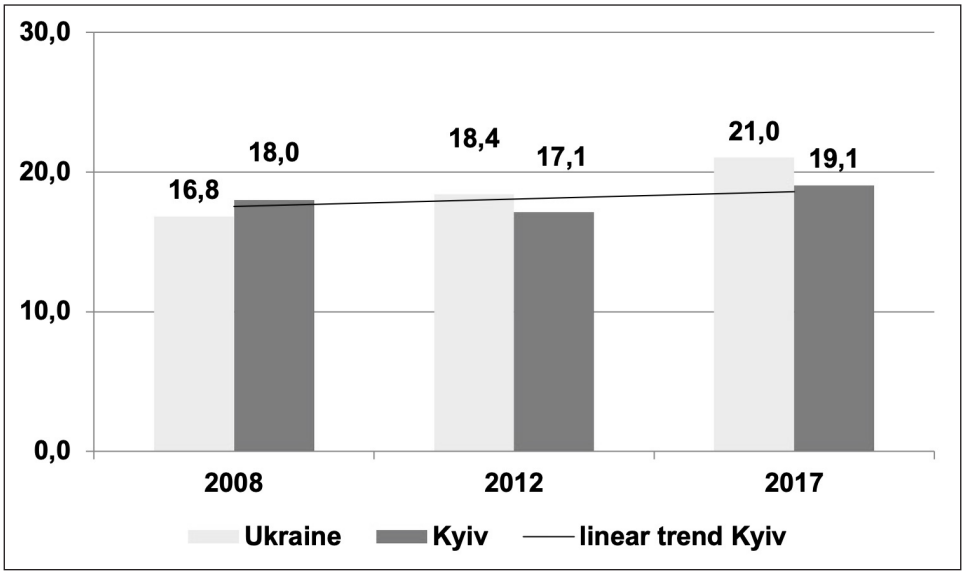

Fig. 2. Relative share of complicated caries among the children, Kyiv, Ukraine, 2008, 2012, 2017 (%) (own development according to the data of statistical reports)

logical prevention among children is an urgent task of stomatological service of Ukraine.

Unsatisfactory stomatological health of children in Ukraine is confirmed by the fact that on average, in 2008, a 12-years-old child had 2.8 teeth treated for caries, filling or extraction. To compare: the same parameter for Germany, Great Britain and Finland made up 0.7 teeth [15].

The regular checkups and regular dental treatment parameters in children showed tendency toward significant decline during 2008-2017 of preventive measures conducted within the children of Kyiv and Ukraine (see table 2.).

So, if in Kyiv in 2008 each child was examined by the stomatologists more than once a year (relative share of the regularly examined children related to all population was 113.7%, in 2017 only 90.8% of all children were regularly examined by stomatologists. These data were considerably lower in all Ukraine (70.9% in 2008 and 56.4% in 2017).

For 10 years total amount of children dental visits has greatly declined, so, despite decrease in the amount of children regularly examined for prevention, the relative share of regularly examined among all children referring for stomatological services, has stayed steady (49- 52% in Kyiv and 42-43% in Ukraine).

Unsatisfactory dental health of children is proved by the fact that among those children who underwent checkups, more than a half in Kyiv (54.6-59.1%) and a half in Ukraine (48.7-49.6%) required dental treatment.

The relative share of the children who were treated during the checkups in 2017 in Kyiv made up 68.0% of the children who required it, and, compared to 2008, it declined by 5.5%. I.e., in 2017 in Kyiv one third of the children (32.0%), who required dental treatment, hadn't received it. In Ukraine the relative share of the children who were treated during periodical checkups related to all children who required treatment, declined from 83.3% in 2008 to 78.5% in 2017.

The assessment of relative share of the children who received dental treatment during regular checkups and upon their referrals showed that in 2017 the percentage

Table 3. Share of patients who received dental treatment upon their referrals or regular checkups in private stomatological establishment in Kyiv and Ukraine 2008,2012, 2017 (own development according to the data of statistical reports)

Region/years	2008	2012	2017	Absolute increase 2017/2008
Relative share of adults who received dental treatment upon their referrals or regular checkups in private stomatological establishments (%)				
Kyiv	12.26	16.04	22.11	9.85
Ukraine	13.45	16.93	22.03	8.59
Relative share of children who received dental treatment upon their referrals or regular checkups in private stomatological establishments (%)				
Kyiv	0.72	1.62	3.65	2.93
Ukraine	0.76	0.75	1.19	0.43

of them in Kyiv corresponded to one third (36.8%) of all children living in Kyiv, while in 2008 all children received dental treatment, sometimes being treated several times a year (113.7% in 2008). The same tendency was observed in Ukraine: decrease of the percentage of the children who received dental treatment after regular checkups and upon their referrals (from 70.9% in 2008 to 33.8% in 2017).

The disadvantages of the dental treatment and prevention management in Kyiv are confirmed by the fact that each third (32.8%) caries case in adults and each fifth (19.1%) case in children is treated as complicated caries.

The dynamic analysis (fig 1, 2.) shows unfavorable tendency toward increase in the relative share of complicated caries treatment among the adults in Kyiv, from 26.5% in 2008 to 32.8% in 2017, and among the children from 18.0% to 19,1%, respectively. This tendency was characteristic for Ukraine in general.

The cause of this is decreased medical service availability and affordability. According to the studies conducted by State Committee of Statistics of Ukraine [16] the share of families in Ukraine where any family member couldn't visit the dentist even though he needed it, during last 12 months, increased from 7,51% in 2013 to 10,13% in 2017. The main cause of stomatological service low availability, as more than 98% of the surveyed suppose, is its high cost in both private and municipal stomatological establishments.

Poor availability of stomatological service and unsatisfactory management of prevention, including the hygienic education, is indirectly supported by those respondents who said that during last 12 months they had referred to the stomatologists in the state (14.5%) and private (7.8%) establishments. So, according to these results, during a year only each fourth Ukrainian refers to the stomatologists and three fourth don't receive stomatological attention during the year.

The results of the conducted study established that during last decade the role of private stomatological establishments in servicing adults has grown.

In Kyiv in 2017 110605 patients over 18years old were treated in private stomatological establishments upon their own referrals or after regular checkups, compared to 2008 this figure has increased 1.3 times. During this period the share of adults who were treated in the private stomatological sector (related to the amount of adult citizens who received this service in all stomatological establishments of Kyiv, both private and state) has increased from 12.26% in 2008 to 22.11% in 2017. The same tendency was characteristic for Ukraine generally (tab.3).

As for the children, in 2017 in Kyiv 7333 children received dental treatment upon their own referrals or after regular checkups in private stomatological establishments which is 3.6% of all children treated in all stomatological establishments. I.e., though during last ten years the number of children treated in private establishments, both in Kyiv and Ukraine, has increased 1.3times, municipal and state stomatological establishments are still the most active and preferred regarding stomatological prevention.

CONCLUSIONS

Authors have found significant decline in preventative measures during 2008-2017, which were rendered by municipal and state stomatological establishments of Kyiv. During 10 years relative share of those who underwent regular checkups has decreased among adults by 16.0% (from 44.0% in 2008 to 28.0% in 2017), and among children – by 22.9% (from 113.7% to 90.8%, respectively), relative share of the patients who received treatment upon their referral or after checkups has decreased among adults by 27.5% (from 44.0% in 2008 to 16.5% in 2017), among children – by 76.9% (from 113.7% to 36.8%, respectively).

The tendency toward increase of the private stomatological establishments' role regarding prevention among the adults has been detected. The share of the patients treated in private establishments among all adult Kyivites has increased from 12.26% in 2008 to 22.11% in 2017.

The prospective further studies may regard substantiation the concepts to the management of preventive stomatological service provided to the big city citizens and developing university stomatological clinic model, basing on the state and private partnership.

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RECOMMENDATIONS
REKOMENDACJE

REKOMENDACJE POLSKIEGO TOWARZYSTWA MEDYCYNY ESTETYCZNEJ I ANTI-AGING DOTYCZĄCE STOSOWANIA WYPEŁNIACZY W TRUDNYCH OKOLICACH: OKO, GŁADZIZNA I SKROŃ

RECOMMENDATIONS OF THE POLISH SOCIETY OF AESTHETIC AND ANTI-AGING MEDICINE CONCERNING THE APPLICATION OF FILLERS IN DIFFICULT AREAS: EYE, GLABELLA AND TEMPLE

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STRESZCZENIE

Medycyna estetyczna to dynamicznie rozwijająca się dziedzina medycyny, a techniki wypełniania są obecnie ważną i szeroko stosowaną procedurą w nowoczesnych metodach terapeutycznych odmłodzenia twarzy.

Celem Rekomendacji PTMEiAA jest poprawa bezpieczeństwa pacjentów, standaryzacja procedur wykonywanych w medycynie estetycznej oraz zdefiniowanie minimalnych wymagań jakościowych podczas wykonywania poszczególnych zabiegów.

Jest to szczególnie ważne w sytuacji, gdy coraz częściej pojawiają się doniesienia o wykonywaniu zabiegów przez osoby nieuprawnione, w miejscach niespełniających wymagań sanitarno-epidemiologicznych do udzielania świadczeń zdrowotnych. Niniejsze opracowanie dotyczy zastosowania wypełniaczy w trudnych okolicach twarzy: okolicy oka, gładzizny i skroni.

SŁOWA KLUCZOWE: medycyna estetyczna, rekomendacje, trudne okolice twarzy, Polskie Towarzystwo Medycyny Estetycznej i Anti-Aging, zastosowanie wypełniaczy w medycynie estetycznej

ABSTRACT

Aesthetic medicine is a dynamically developing field of medicine and filling techniques are currently an important and widely used procedure in modern therapeutic methods of facial rejuvenation. The aim of the PTMEiAA Recommendation is to improve patient safety, standardize procedures performed in aesthetic medicine and define minimum quality requirements during individual procedures. This is particularly important in the situation where there are more and more reports of the performance of treatments by unauthorized persons in places that do not meet the sanitary and epidemiological requirements to provide health services. The present study concerns the use of fillers in difficult facial areas: around the eye, glabella and temples.

KEY WORDS: aesthetic medicine, recommendations, difficult areas of the face, Polish Society of Aesthetic and Anti-Aging Medicine, application of fillers in aesthetic medicine

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1. WSTĘP

Polskie Towarzystwo Medycyny Estetycznej i Anti-Aging obchodziło w 2018 roku 25 rocznicę swojej działalności. Przez 25 lat Towarzystwo koncentrowało się na edukacji lekarzy praktykujących medycynę estetyczną, poprawie bezpieczeństwa pacjentów oraz na uporządkowaniu wytycznych z zakresu medycyny estetycznej. Medycyna estetyczna to dynamicznie rozwijająca się dziedzina medycyny, a techniki wypełniania są obecnie ważną i szeroko stosowaną procedurą w nowoczesnych metodach terapeutycznych odmłodzenia twarzy.

Celem Rekomendacji PTMEiAA jest poprawa bezpieczeństwa pacjentów, standaryzacja procedur wykonywanych w medycynie estetycznej oraz zdefiniowanie minimalnych wymagań jakościowych podczas wykonywania poszczególnych zabiegów. Jest to szczególnie ważne w sytuacji, gdy coraz częściej pojawiają się doniesienia o wykonywaniu zabiegów przez osoby nieuprawnione w miejscach niespełniających

wymagań sanitarno-epidemiologicznych do udzielania świadczeń zdrowotnych i lekarskich czynności nieleczniczych.

Zastosowanie wypełniaczy w procedurach medycyny estetycznej wymaga dokładnej znajomość anatomii, co umożliwia bezpieczne wykonywanie zabiegów mających na celu odbudowę utraconej objętości tkanek twarzy [1]. Wstrzyknięcie wypełniaczy w powierzchowne warstwy skóry, z wyjątkiem regionu gładzizny, stanowi minimalne ryzyko, dlatego też w większości przypadków procedury są wykonywane powierzchownie, w tkance podskórnej. Jednakże rozwój technik wypełniania, ich ewolucja oraz dogłębna znajomość anatomii umożliwiają podawanie materiału wypełniającego w głębsze warstwy. Podanie materiału wypełniającego w bruzdy utrwalone, nierówności czy blizny jest obecnie bardzo popularną, skuteczną i małoinwazyjną metodą opóźniającą występowanie widocznych efektów starzenia.

2. MIEJSCE WYKONANIA ZABIEGU I UPRAWNIENIA DO WYKONANIA ZABIEGU

Zabieg powinien zostać wykonany w miejscu spełniającym wymogi ustawy o działalności leczniczej (Dz.U. 2015 poz. 618 ze zm.), wyposażonym w produkty lecznicze, wyroby medyczne, aparaturę i sprzęt medyczny odpowiedni do rodzaju i zakresu wykonywanych zabiegów oraz zestaw do udzielania pierwszej pomocy lekarskiej. Osobą uprawnioną do wykonania zabiegu jest lekarz posiadający aktualne prawo wykonywania zawodu, przeszkolony z technik podawania wypełniaczy. Dla bezpiecznego wykonania zabiegu, lekarz powinien posiadać wiedzę na temat anatomii leczonego obszaru, znać wskazania i przeciwskazania do zabiegu oraz możliwe powikłania.

3. WSKAZANIA I PRZECIWSKAZANIA

Wskazania:

Prowadzący do zmian w utkaniu skóry i utraty objętości deficyt tkanek miękkich np. widoczna dolina łez, cienie pod oczami, dół skroniowy, utrata objętości łuku brwiowego itp.

Przeciwwskazania:

- Nierealne oczekiwania pacjenta
- Uczulenie na składniki preparatu
- Zaburzenia krzepnięcia
- Planowana intensywna aktywność fizyczna w bezpośrednim czasie po zabiegu
- Choroby autoimmunologiczne
- Zakażenie bakteryjne oraz stan zapalny występujące w planowanym miejscu podania
- Infekcja wirusowa (np. opryszczka)
- Przepuklina przegrody oczodołowej
- Ciężka elastoza (duże „worki" pod oczami), obecność poduszeczek jarzmowych

4. PRZYGOTOWANIE PACJENTA DO ZABIEGU

4.1 WYWIAD

W trakcie wywiadu należy omówić z pacjentem wskazania i przeciwskazania do wykonania zabiegu oraz możliwe powikłania. Lekarz powinien w sposób szczególny wypełnić obowiązek informacyjny wynikający z *Ustawy o prawach pacjenta i Rzeczniku Praw Pacjenta* (art. 16) oraz uzyskać pisemną zgodę pacjenta na zabieg (art. 18 ust. 1). Dobrą praktyką jest, gdy zabiegu nie wykonuje się w dniu pierwszej wizyty (powinno upłynąć co najmniej 24 godziny od czasu wizyty, aby była możliwość przeanalizowania podanych przez lekarza informacji odnośnie zabiegu i podpisania świadomej zgody na proponowaną procedurę).

4.2 DOKUMENTACJA MEDYCZNA

Dokumentacja medyczna powinna być prowadzona zgodnie z Rozporządzeniem Ministra Zdrowia z dnia 9 listopada 2015 r. w sprawie rodzajów, zakresu i wzorów dokumentacji medycznej oraz sposobu jej przetwarzania (Dz.U. 2015 poz. 2069 z pózn. zm.) i zawierać w szczególności dokumentację zdjęciową (przed i po zabiegu), informację o rodzaju i ilości użytego wypełniacza (wraz z numerem serii i datą ważności) oraz formularz świadomej zgody podpisywany i datowany przez pacjenta przed każdym zabiegiem.

4.3 PRZYJMOWANIE LEKÓW W OKRESIE OKOŁO ZABIEGOWYM

Przed zabiegiem pacjent powinien odstawić przyjmowane leki – o ile nie ma ku temu istotnych przeciwskazań wynikających z leczenia choroby podstawowej – leki i suplementy, które mają działanie antykoagulacyjne, takie jak: aspiryna, leki z grupy NLPZ, warfaryna, klopidogrel, arnica, imbir, żeń-szeń, miłorząb japoński, witamina E, dziurawiec. Nie jest konieczne znieczulenie pacjenta, choć dla poprawienia komfortu zabiegu można nałożyć krem znieczulający w okluzji na około 40–60 min. Należy upewnić się, czy pacjent nie jest uczulony na środki znieczulające.

4.4 DEZYNFEKCJA SKÓRY

Przed wykonaniem iniekcji – po uprzednim zmyciu makijażu – należy dokonać dezynfekcji skóry preparatem o szerokim spektrum działania poprzez bezpośrednie 2–3-krotne spryskanie powierzchni skóry lub przemycie skóry – od wewnątrz do zewnątrz pola zabiegu – z użyciem jałowego gazika nasączonego preparatem do dezynfekcji.

5. MATERIAŁ WYPEŁNIAJĄCY

5.1 KWAS HIALURONOWY

Materiałem najczęściej stosowanym obecnie przez lekarzy medycyny estetycznej, jako wypełniacz jest kwas hialuronowy (HA). Jest on najbardziej rozpowszechnionym biopolimerem naturalnie występującym w ludzkim organizmie, co przekłada się na jego bezpieczeństwo. Bez względu na źródło pochodzenia, czy z kultur bakteryjnych, zwierząt lub ludzi, jego struktura jest identyczna. Niezmodyfikowany, naturalny hialuronian szybko ulega rozkładowi przez

hialuronidazę i eliminowany jest przez układ limfatyczny i metabolizm wątrobowy. Dlatego też, w celu wytworzenia lepkiego, sprężystego materiału o zwiększonej trwałości poddano go modyfikacji i usieciowano. Wiążąc cząsteczki wody nadaje on skórze i tkance łącznej objętość. Jego lekka, łatwo dającą się modelować konsystencja, określony czas działania, duża zdolność do wiązania wody, dzięki czemu już niewielka ilość preparatu może wypełnić widoczne ubytki oraz łatwości implantacji spowodowały, iż jest on niezwykle skuteczny [2].

Stężenie kwasu hialuronowego oraz stopień jego usieciowania w preparacie decyduje o miejscu jego zastosowania. Niskousieciowany kwas hialuronowy o dużych właściwościach plastycznych jest idealny do iniekcji tuż pod skóra właściwą, np. w okolicy gładzizny czy oka [3]. Do głębokiego podania na kość, np. w okolicę skroni nadaje się kwas średnio usieciowany, o średnim stężeniu, o niezbyt dużej lepkości i elastyczności.

5.2 INNE WYPEŁNIACZE

5.2.1 HYDROKSYAPATYT WAPNIA

Pierwotnie został zarejestrowany przez FDA w 2006 do leczenia ubytku tkanki podskórnej u chorych na HIV a od 2009 wskazania zostały rozszerzone na pozostałych pacjentów. Hydroksyapatyt wapnia stanowi w preparacie 30% (70% to żel stanowiący nośnik), dlatego po 6 miesiącach obserwuje się niewielki spadek efektu wypełnienia [4] (po tym czasie żel zanika). Hydroksyapatyt wapnia można podawać nad okostną lub podskórnie, choć głębokie podanie wiąże się z mniejszym ryzykiem wystąpienia guzków. Należy zwrócić szczególną uwagę podczas wycofywania igły ze względu na ryzyko powstawania guzków, związanych z depozycją hydroksyapatytu w skórę [5]. Niektórzy z powodu dyskomfortu związanego z podawaniem preparatu zalecają mieszanie hydroksyapatytu wapnia z lignokainą [6].

6. WYKONANIE ZABIEGU

6.1 OKOLICA OKA: POWIEKA GÓRNA I ŁUK BRWIOWY

Proces starzenia się twarzy jest złożony i obejmuje zmiany w obrębie skóry, podskórnej tkanki tłuszczowej, mięśni mimicznych oraz podłoża kostnego. Okolica oka stanowi szczególne wyzwanie dla lekarza medycyny estetycznej. Jest to jedno z miejsc, gdzie zmiany związane z wiekiem są najszybciej widoczne. Proces starzenia polegający na resorpcji kości twarzoczaszki w pierwszej kolejności zachodzi w oczodole, zwłaszcza w jego górno-środkowej i dolno-bocznej części, co prowadzi do wydłużenia skośnego wymiaru oczodołu [7]. Wraz z wiekiem postępuje proces zanikania mięśni szkieletowych. Mięśnie mimiczne starzeją się w specyficzny sposób: następuje ich wydłużenie z jednoczesnym wzrostem napięcia. Zwiększone napięcie mięśni prowadzi do ich stałego przykurczu, co w obrębie mięśni mimicznych oka powoduje powstanie tak zwanych „kurzych łapek", zmarszczek wywołanych przez mięsień okrężny oka oraz zmarszczek glabelarnych („lwia zmarszczka"), wywołanych przez mięsień marszczący brwi i włókna przyśrodkowe i górne mięśnia okrężnego oka, tworzące mięsień obniżacz brwi [8]. „Kurze łapki" są dodatkowo pogłębiane przez opadnięcie podoczodołowego ciała tłuszczowego. Osłabieniu ulega przegroda oczodołowa, utrzymująca wraz z mięśniem okrężnym oka nad- i podgałkową tkankę tłuszczową w głębi oczodołu. Jednocześnie mięsień okrężny oka zmniejsza objętość, co prowadzi do zmniejszenia skuteczności działania podporowego [9]. Dochodzi do powstania przepukliny tkanki tłuszczowej nadgałkowej w okolicy górnej powieki i pozaprzegrodowego ciała tłuszczowego do dolnej powieki („worki po oczami"). Dochodzi także do opadnięcia podoczodołowego ciała tłuszczowego w kierunku policzka i fałdu nosowo-wargowego [10].

6.1.1 WARUNKI ANATOMICZNE

6.1.1.1 SKÓRA

Skórę okolicy oczodołowej można podzielić na kilka obszarów. Należą do nich: powieka górna, powieka dolna, kąt oka przyśrodkowy, kąt oka boczny oraz brew. Skóra powiek jest bezpośrednio połączona z częścią powiekową mięśnia okrężnego oka.

6.1.1.2 MIĘŚNIE

Do grupy mięśni otoczenia szpary powiek należą mięsień okrężny oka, mięsień marszczący brwi, mięsień podłużny i mięsień obniżacz brwi. Mięsień okrężny oka składa się z trzech części: oczodołowej, powiekowej i łzowej. Przedmiotem zabiegów w medycynie estetycznej jest jedynie część oczodołowa. Włókna mięśnia okrężnego oka ulegają w części przyśrodkowej i górnej częściowemu wymieszaniu z włóknami mięśnia marszczącego brwi i z mięśniem podłużnym. Włókna przyśrodkowo-górnego odcinka biegną do skóry do przyśrodkowej części brwi, tworząc mięsień obniżacz brwi. Po stronie bocznej mięsień okrężny oka pokrywa boczną krawędź oczodołu. Na stronie bocznej policzka sąsiaduje z mięśniem jarzmowym mniejszym. Część oczodołowa mięśnia okrężnego oka pociąga brwi ku dołowi oraz pomaga przy zaciskaniu powiek. Jest antagonistą mięśnia czołowo-potylicznego. Skurcz mięśnia obniżacza brwi powoduje załamanie się przyśrodkowej części brwi ku dołowi [11]. Mięsień podłużny rozpoczyna się na kości nosowej, a kończy w skórze gładzizny. Jego skurcz pociąga skórę ku dołowi, wywołując poprzeczny fałd u nasady nosa. Jest antagonistą m. czołowo-potylicznego. Mięsień marszczący brwi rozpoczyna się na kości czołowej, a jego włókna kończą się w skórze powyżej brwi. Mięsień pociąga skórę do wewnątrz i ku dołowi, powodując dwa (czasem trzy) pionowe fałdy między brwiami, nadając twarzy wyraz złości i zniecierpliwienia (brew Laokoona, lwia bruzda) [11]. Praca mięśni w okolicy oka jest główną przyczyną pojawiania się miejscowych zmian w utkaniu skóry i tkanki podskórnej widocznych w formie zmarszczek.

6.1.1.3. TKANKA TŁUSZCZOWA I POZOSTAŁE STRUKTURY

Pod mięśniem okrężnym oka i pod znajdującą się pod nim tkanką tłuszczową znajduje się przegroda oczodołowa, zbudowana z tkanki łącznej będącej przedłużeniem okostnej kości, z których składa się oczodół. Stanowi ona powięź tylną mięśnia okrężnego oka. Odpowiada za utrzymanie we właściwym miejscu tkanki tłuszczowej oczodołu. Ciało tłuszczowe okolicy górnej powieki to ciało tłuszczowe pozaoczodołowe (ROOF – *retroorbicularis oculi fat*) znajdujące się na krawędzi łuku brwiowego pod m. okrężnym oka. Gdy jest ono powiększone, uwypukla okolicę brwiową, przysłaniając fałd powiekowy górny.

6.1.1.4. NACZYNIA KRWIONOŚNE I GRUCZOŁ ŁZOWY

W trakcie iniekcji w okolicy brwi należy mieć na względzie tętnicę i żyłę nadoczodołową, która przebiega środkowo powyżej gałki ocznej i opuszcza oczodół przez otwór nadoczodołowy oraz tętnicę i żyłę nadbloczkową, które opuszczają oczodół w okolicy kąta przyśrodkowego. Podanie materiału wypełniającego do tętnicy nadbloczkowej, która jest gałęzią tętnicy ocznej może na skutek wstecznego przepływu wywołać ślepotę, spowodowaną zatorem tętnicy środkowej siatkówki. Podczas korekcji okolicy brwi i powieki górnej należy również uważać na gruczoł łzowy, którego część oczodołowa leży na mięśniu dźwigacza powieki górnej i sąsiaduje z tłuszczem oczodołu [12, 13].

6.1.2 MIEJSCA INIEKCJI

Uzasadnieniem użycia wypełniaczy w tym obszarze jest zanik pozaoczodołowego ciała tłuszczowego (ROOF), co daje efekt „pustego oczodołu".

Wypełniacze podawać należy w bocznej części brwi, w celu uzyskania wypełnienia górnej części oczodołu. W odmładzaniu okolicy brwi zaleca się stosować preparaty kwasu hialuronowego ze względu na możliwą częściową odwracalność metody.

6.1.3 TECHNIKA INIEKCJI

6.1.3.1 KANIULA

Kaniula pozwala na bezpieczniejsze wykonanie zabiegu z uwagi na mniejsze ryzyko uszkodzenia naczyń i nerwów [14]. Zaleca się znieczulić miejsce wprowadzenia kaniuli. Po wytworzeniu kanału za pomocą igły bezpośrednio przy bocznym końcu brwi, wprowadza się kaniulę 25 G głęboko, kierując się na okostną górnego brzegu oczodołu. Materiał należy zostawiać głęboko w okolicy przedokostnowej, w trzech przejściach: nad brwią, pod brwią i na samej linii brwi. Odtwarzając tkankę górnej części oczodołu, należy użyć techniki wachlarzowej, zostawiając materiał liniowo. Odtwarzając tkankę tłuszczową oczodołu, najwięcej materiału należy zostawić w przyśrodkowej i centralnej części brwi.

6.1.3.2 IGŁA

Inną techniką jest podanie materiału igłą zagiętą pod kątem 45 z zagięciem skierowanym ku górze, podskórnie do poduszeczki tłuszczowej brwi. Podawanie materiału następuje wówczas przed dalszym włożeniem igły, dzięki czemu odczucia bólowe są mniejsze, jeśli materiał zawiera lignokainę oraz zminimalizowane zostaje ryzyko powstawania siniaków [15]. Miejsce podania wypełniacza należy delikatnie rozmasować. Nie należy podawać dużych ilości wypełniacza, większość autorów zaleca nie więcej niż 0,5 ml na stronę w przypadku kwasu hialuronowego [16]. Kwas hialuronowy podawany w tej okolicy powinien być średnio usieciowany, aby zapobiec wystąpieniu dużych obrzęków.

6.2 OKOLICA OKA: POWIEKA DOLNA I DOLINA ŁEZ

6.2.1 WARUNKI ANATOMICZNE

6.2.1.1 NACZYNIA I NERWY

W tej okolicy należy zwrócić szczególną uwagę na otwór podoczodołowy, gdzie mają ujście tętnica podoczodołowa będąca gałęzią tętnicy szczękowej i nerw podoczodołowy. Nerw podoczodołowy jest gałęzią nerwu szczękowego, który jest nerwem czuciowym. Uszkodzenie nerwu podoczodołowego może spowodować przejściową anestezję lub parestezje środkowej części twarzy [17]. Należy również zwrócić uwagę na tętnicę kątową, będącą końcową gałęzią tętnicy twarzowej. Tętnica kątowa zespala się z tętnicą grzbietową nosa, która z kolei jest gałęzią tętnicy ocznej.

6.2.1.2 TKANKA TŁUSZCZOWA

W okolicy powieki dolnej znajdują się kompartmenty tłuszczowe powierzchowne i głębokie. Powierzchowne kompartmenty tłuszczowe są zlokalizowane między skórą a SMAS (Superficial Muscular Aponeurotic System). Należy do nich leżący nad mięśniem okrężnym oka i nad SMAS tłuszcz podoczodołowy. Powierzchowny tłuszcz podoczodołowy nie przechodzi płynnie w zewnętrzny kompartment tłuszczowy policzka, ponieważ oddziela je więzadło jarzmowo-skórne. Podanie wypełniaczy bezpośrednio do powierzchownego kompartmentu tłuszczowego skutkuje powstaniem obrzęku (ang. *malar edema*), utrzymującego się przez wiele miesięcy.

W procesie starzenia powierzchowny tłuszcz podoczodołowy wraz z wiotczejącym mięśniem okrężnym oka tworzą tzw. „worki" pod oczami (ang. festoons).

6.2.1.2.1 KOMPARTMENTY GŁĘBOKIE

Głęboki kompartment tłuszczowy okolicy powieki dolnej znajduje się pod SMAS oraz pod m. okrężnym oka i przylega do okostnej. Jest to ciało tłuszczowe podoczodołowe (ang. *suborbicularis oculi fat*, SOOF). Należą tu dwa kompartmenty: podoczodołowy tłuszcz przyśrodkowy (ang. medial SOOF) i boczny (ang. *lateral* SOOF) [18]. Boczny SOOF może być widoczny spod mięśnia okrężnego oka, tworząc tak zwaną poduszkę jarzmową.

Górna granica SOOF wyznacza dolinę łez na powierzchni skóry. Tworzy ją więzadło podtrzymujące oczodołu, którego zadaniem jest podpieranie mięśnia okrężnego oka. Zaczyna się na okostnej oczodołu, 1-2 mm poniżej jego dolnej krawędzi i przechodząc przez m. okrężny oka, kończy się w skórze [19]. Według niektórych autorów, więzadło nie kończy się w skórze, ale na powięzi m. okrężnego oka [20]. Okolica doliny łez stanowi zagłębienie biegnące ukośnie w okolicy podoczodołowej od przyśrodkowego kąta szpary powiekowej do linii środkowej źrenicy. W tym miejscu mięsień okrężny oka nie jest pokryty tłuszczem podoczodołowym, ale przebiega bezpośrednio pod skórą. Uwidocznienie doliny łez następuje wraz z atrofią skóry i mięśnia okrężnego oka. Jeśli dojdzie przy tym do przepukliny przegrody oczodołowej i wysunięcia się tłuszczu pozaprzegrodowego, nawis tkanek zostaje „zatrzymany" przez więzadło podtrzymujące oczodołu. Zjawisko to uwydatnia dolinę łez [21].

Dolną granicę SOOF stanowi więzadło jarzmowo-skórne, biegnące od policzkowego brzegu mięśnia okrężnego oka do powierzchownego układu mięśniowo-rozcięgnowego twarzy w okolicy powięzi żwacza [21]. Podoczodołowy tłuszcz ograniczony od góry i od dołu więzadłami kostno-skórnymi ma dużą tendencję do obrzęków. Wypełnienie doliny łez ma na celu odtworzenie objętości w zakresie SOOF przyśrodkowego i bocznego, przy czym lekarz wykonujący zabieg musi być pewny, że materiał został podany głęboko na kość poniżej dolnego brzegu oczodołu [22].

6.2.2 MIEJSCE I TECHNIKA INIEKCJI

Przed wykonaniem zabiegu należy oznaczyć dolny brzeg oczodołu oraz miejsce otworu podoczodołowego, który znajduje się około 8 milimetrów poniżej dolnego brzegu oczodołu w linii środkowej źrenicy. Pacjenta należy ułożyć w pozycji półsiedzącej pod kątem około 45°, wtedy dolina łez jest najlepiej widoczna. W okolicy dolnej powieki znajduje się splot naczyń, dlatego przed zabiegiem można schłodzić okolicę powieki dolnej okładami z lodu, przez około 10 minut, w celu uniknięcia krwawienia. Wypełniacz powinien być podawany głęboko na kość w minimalnych ilościach, aby rezultat był jak najbardziej naturalny oraz aby uniknąć obrzęku okolicy jarzmowej, grudek i przeświytywania materiału przez skórę. Wypełniacze należy podawać pod mięsień okrężny oka. Materiał można podawać igłą lub kaniulą [23].

6.2.2.1 IGŁA

Zaleca się podawać materiał głęboko na okostną, poniżej dolnej krawędzi oczodołu. Wkłucie igły zazwyczaj jest prostopadłe do powierzchni skóry. Należy końcem igły wyczuć kość. Zaleca się użycie igły 29 lub 30 G o długości 25 mm, aby igła mogła dosięgnąć kości oczodołu. Podanie materiału powinno się odbywać techniką mikrodepozytów lub wstecznego wycofywania, w ilości 0,05–0,1 ml na punkt. Nie należy przekraczać objętości 0,2 ml na stronę. Po 2–3 tygodniach należy przeprowadzić kontrolę i ewentualnie uzupełnić materiał.

Pierwsze miejsce wkłucia zaleca się wykonać przyśrodkowo od otworu podoczodołowego, w połowie odległości między kątem wewnętrznym oka a otworem podoczodołowym, około 1 cm poniżej dolnego brzegu oczodołu. Drugie miejsce wkłucia powinno być wykonane nieco bocznie od otworu podoczodołowego. Trzecia iniekcja powinna być wykonana tylko wówczas, gdy stwierdza się ubytek tkanki okolicy jarzmowej. Miejsce wkłucia powinno się wówczas znaleźć na wyniosłości jarzmowej [20, 22]. Po zabiegu należy wykonać delikatne rozmasowanie materiału.

6.2.2.2 KANIULA

Podanie kaniulą jest bezpieczniejsze z uwagi na mniejsze niebezpieczeństwo uszkodzenia naczyń i nerwów [14]. Kaniula, podobnie jak igła, powinna być wprowadzana głęboko pod mięsień okrężny oka, w okolicę nadokostnową. Jedno z miejsc iniekcji znajduje się 1,5–2 cm w linii pośrodkowej źrenicy bądź bocznie od otworu podoczodołowego. Materiał jest podawany techniką liniową wsteczną. Zaleca się użycie kaniuli 25–27 G [15]. Ilość kwasu hialuronowego podanego na stronę zależy od głębokości ubytku tkanek, jednak nie powinna przekraczać 0,25 ml. Najczęściej jest to wystarczająca objętość kwasu na stronę [16]. Po zabiegu zaleca się rozmasowanie podanego materiału. Po 2–3 tygodniach należy przeprowadzić kontrolę i ewentualnie uzupełnić materiał.

1.3 GŁADZINA

1.3. 1 WARUNKI ANATOMICZNE

1.3.0.1. GŁADZINA

To wyniosłość leżąca pomiędzy łukami brwiowymi jest miejscem, gdzie przenikają się liczne naczynia krwionośne. Górna powierzchnia grzbietu nosa i środkowa część brwi stanowi jej granicę dolną. Linie pionowe, 1,5 cm od linii środkowej źrenicy przyśrodkowo stanowią granice boczne. Jeśli je połączymy, 1,5 cm powyżej górnej granicy brwi, w kierunku czoła, uzyskamy granicę górną. Na szczególną uwagę w tej okolicy zasługują: tętnica nadoczodołowa i tętnica nadbloczkowa będąca gałęzią tętnicy twarzowej. W tym regionie – jak i w segmencie czołowym – istnieją również tętnice, które mogą być zespolone z tętnicami końcowymi zaopatrującymi narząd wzroku i siatkówkę. Zaleca się zachowanie szczególnej ostrożności podczas podawania wypełniaczy w celu zmniejszenia zmarszczek w tej okolicy twarzy. Embolizacja naczyń może prowadzić do natychmiastowej i czasami nieodwracalnej ślepoty, która może być nawet dwustronna.

1.3.1. MIEJSCE I TECHNIKA INIEKCJI

W przypadku zabiegu wykonywanego igłą nie ma specjalnych wytycznych, co do miejsc iniekcji. Należy zachować szczególną ostrożność w okolicy przebiegu naczyń nadoczodołowych i nadbloczkowych. Wypełniacz należy

podawać płytko, liniowo. Zabieg wykonany igłą wiąże się z większą liczbą wkłuć i większym dyskomfortem dla pacjenta. W przypadku użycia kaniuli, choć ta technika nie jest preferowana, należy rozważyć podanie głębokie na kość w formie bolusa, który następnie należy rozmasować. Miejsca iniekcji kaniuli powinny być oddalone od typowych miejsc przebiegu naczyń krwionośnych. Podanie materiału punktowo, w pojedynczych bolusach może zwiększyć ryzyko powstania nierówności. Należy zachować szczególną ostrożność w leczeniu tej okolicy ze względu na ryzyko poważnych powikłań.

1.4. SKROŃ

Zagłębianie się okolicy skroni jest jednym z objawów starzenia się twarzy występującym częściej u kobiet. Zagłębienie tkanek w okolicy dołu skroniowego związane jest z zanikiem tkanki tłuszczowej (tłuszczu kompartmentu skroniowo-policzkowego, ale głównie ciała tłuszczowego skroniowego i ciała tłuszczowego policzka), mięśnia skroniowego i kości skroniowej [10, 24–27].

1.4.1. WARUNKI ANATOMICZNE

Należy zwrócić uwagę na wzajemną topografię przebiegających w obszarze skroni tętnic, żył i nerwów, a w szczególności [10, 13, 25–28]:

- Tętnic: gałęzi czołowej tętnicy skroniowej powierzchownej, tętnicy jarzmowo-oczodołowej, tętnic skroniowych głębokich, tętnicy nadoczodołowej,
- Żył: gałęzi czołowej żyły skroniowej powierzchownej, żyły jarzmowo-oczodołowej, żył skroniowych głębokich, żyły nadoczodołowej,
- Nerwów: gałęzi skroniowych nerwu twarzowego, gałęzi jarzmowych nerwu twarzowego, gałęzi bocznych nerwu nadoczodołowego, nerwów skroniowych głębokich.

W przypadku użycia igły, podczas iniekcji napotyka ona na następujące struktury anatomiczne: skórę, ciało tłuszczowe skroniowe powierzchowne wchodzące w skład skroniowo-policzkowego kompartmentu tłuszczowego [29], blaszkę powierzchowną powięzi skroniowej, ciało tłuszczowe skroniowe, blaszkę głęboką powięzi skroniowej, mięsień skroniowy (a do przodu od mięśnia – ciało tłuszczowe policzka [Bichata]), pokrytą okostną część łuskową kości skroniowej (a do przodu od kości skroniowej – skrzydło większe kości klinowej [10, 28].

1.4.2. MIEJSCE INIEKCJI

Skóra w okolicy skroni jest cienka, z dużą ilością tkanki łącznej o gęstej konsystencji, z dość dobrze widocznymi powierzchniowymi naczyniami (tętnicą i żyłą skroniową) [13, 24].

Przed iniekcją należy oznaczyć przebieg tętnicy skroniowej, podobnie jak obszar o wysokości około 1,5cm przebiegający wzdłuż i powyżej łuku jarzmowego w związku z przebiegiem w tej okolicy żył skroniowych środkowych [24, 25, 27, 30]. Należy także wyznaczyć kresę skroniową biegnącą ku górze od wyrostka jarzmowego kości czołowej a następnie ku tyłowi tuż nad szwem klinowo-czołowym [10]. Kresa skroniowa ogranicza od góry i przyśrodka brzeg obszaru bezpiecznego podania. Nie należy przekraczać linii włosów i wykonywać iniekcję ku przodowi od tej linii [24, 26].

1.4.3. TECHNIKA INIEKCJI

1.4.3.1. IGŁA

Po wyznaczeniu bezpiecznego obszaru iniekcji igłę wprowadzamy około 1–1,5 cm do tyłu od bocznego brzegu brwi, nakłuwając skórę prostopadle. Należy końcem igły wyczuć kość, a następnie zaaspirować w celu wykluczenia nakłucia naczynia [24]. Należy mieć na uwadze, że w przypadku użycia igieł o małej średnicy brak krwi nie zawsze oznacza, iż nie znajdujemy się w naczyniu. Najlepiej użyć igły o rozmiarze 27-30 G i długości 13-19 mm. Wypełniacz podaje się powoli w formie bolusa w objętości około 0,5 ml na stronę (nie więcej niż 1 ml na stronę). Po podaniu należy rozmasować leczony obszar w celu równomiernego rozmieszczenia wypełniacza [24, 26, 30].

1.4.3.2. KANIULA

Zaleca się wykorzystać kaniulę do podania powierzchownego w ciało tłuszczowe skroniowe powierzchowne wchodzące w skład skroniowo-policzkowego kompartmentu tłuszczowego [29]. Podanie głębokie jest bolesne dla pacjenta, dlatego nie jest zalecane [24]. Przed wprowadzeniem pod skórę kaniuli, należy znieczulić miejsce jej wprowadzenia oraz wykonać igłą 22G kanał w skórze ułatwiający jej wprowadzenie. Kaniulę o rozmiarze 25-27 G wprowadza się w okolicy kości jarzmowej i kieruje się podskórnie w kierunku dołu skroniowego. Materiał wprowadza się w technice wachlarzowej podczas wycofywania kaniuli. Następnie miejsce podania należy rozmasować w celu optymalnego rozmieszczenia wypełniacza.

1.5. ZALECENIA POZABIEGOWE

Postępowanie pozabiegowe jest istotne dla uzyskania optymalnych efektów zabiegu. Pacjent powinien przez około 2 tygodnie powstrzymać się od ekspozycji na wysokie czy niskie temperatury, jak sauna, opalanie czy jazda na nartach. Zalecana jest kontrola po 2 tygodniach.

1.6. POWIKŁANIA

Najczęściej w wyniku iniekcji występuje miejscowy obrzęk, ból czy podbiegnięcia krwawe, zwykle szybko ustępujące [13, 24, 27, 30]. Rzadziej obserwuje się hiperkorekcję lub nierównomierne rozprowadzenie wypełniacza najczęściej będące wynikiem podania zbyt dużej ilości wypełniacza lub nieodpowiednim jego rozprowadzeniem [31]. W piśmiennictwie światowym opisano kilka przypadków utraty widzenia w wyniku podania donaczyniowego materiału wypełniającego (najczęściej autologicznego tłuszczu) [24].

1.6.1. ZDARZENIA NIEPOŻĄDANE W MIEJSCU INIEKCJI

Najczęściej występującym zdarzeniem niepożądanym są związane z iniekcją i lokalnie występujące: obrzęk, zaczerwienienie, swędzenie oraz sińce. Objawy te są łagodne i ustępują w ciągu następnych kilku dni. Ból należy do częstych objawów niepożądanych. W celu zmniejszenia dolegliwości bólowych należy używać cienkich igieł, stosować znieczulenie miejscowe oraz zimne okłady przed zabiegiem i bezpośrednio po nim [32, 33].

Należy zaprzestać przyjmowania aspiryny, leków z grupy NLPZ, Miłorzębu japońskiego, witaminy E, żeńszenia, ziela dziurawca dla zmniejszenia częstości występowania obrzęków i sińców. Można stosować wyciąg z kasztanowca, witaminę K i bromelinę przed i po zabiegu [32, 34, 35].

1.6.2. PODANIE DOCZASZKOWE

Jest to niezwykle rzadkie powikłanie, opisywane podczas iniekcji głębokich najczęściej w okolicy skroni za pomocą igły. Dlatego należy zachować szczególną ostrożność podczas leczenia tej okolicy.

1.6.3. EFEKT TYNDALA

Efekt Tyndala występuje w wyniku zbyt płytkiego umiejscowienia kwasu hialuronowego i objawia się błękitnym przebarwieniem skóry [32, 36, 37].

1.6.4. REAKCJE NADWRAŻLIWOŚCI

Reakcje nadwrażliwości na wypełniacz występują niezmiernie rzadko (0,8%) i objawiają się zaczerwienieniem, obrzękiem oraz stwardnieniem w miejscu implantacji, czasami w tkankach otaczających [32, 38].

1.6.5. INFEKCJE

W związku z przerwaniem ciągłości skóry istnieje ryzyko infekcji bakteryjnej, wirusowej czy grzybiczej. Dlatego należy zwrócić szczególną uwagę na występujące w wywiadzie zabiegi dentystyczne, przewlekłe zapalenie zatok czy planowane zabiegi dentystyczne w najbliższych 2 tygodniach [32].

1.6.6. OPRYSZCZKA

Nierzadkim powikłaniem jest nawrót zakażenia opryszczką szczególnie podczas wypełniania ust, dlatego pacjenci cierpiący na częste nawroty opryszczki powinni przyjmować dwa lub trzy razy dziennie po 400mg acykloviru dwa dni przed i trzy dni po zabiegu. Wykonywanie zabiegów z wypełniaczami jest przeciwskazane w przypadku aktywnej opryszczki [32, 38].

1.6.7. ROPIEŃ I ZAPALENIE TKANKI ŁĄCZNEJ.

Wystąpienie czerwonych guzków z towarzyszącym bólem i napięciem skóry w okresie 3–14 dni po zabiegu może świadczyć o infekcji (ropniu) w miejscu podania wypełniacza [32, 39].

1.6.8. BIOFILM

Infekcja bakteryjna po podaniu wypełniacza może sprzyjać tworzeniu biofilmu, który znacznie utrudnia wygojenie [32, 40].

1.6.9. ZIARNINIAKI

Do powstania ziarniniaków może dojść w przebiegu przewlekłej reakcji zapalnej będącej wynikiem odpowiedzi immunologicznej organizmu na ciało obce. Patogeneza powstawania ziarniniaków nie jest do końca znana. Może to być związane z odpowiedzią na śladowe ilości białek zawartych w wypełniaczu. Zjawisko to występuje niezmiernie rzadko w 0,02–0,4% przypadków [32, 41, 42].

1.6.10. ZAMKNIĘCIE ŚWIATŁA NACZYNIA

Zamknięcie naczynia jest bardzo groźnym powikłaniem po użyciu wypełniaczy. Może objawiać się martwicą skóry bezpośrednio w miejscu podania lub odległym ostrym niedokrwieniem (utrata widzenia, niedokrwienie obszarów mózgu). Zamknięcie naczynia tętniczego w wyniku bezpośredniego podania w światło naczynia objawia się natychmiastowym zblednięciem skóry, silnym bólem, a nieleczone prowadzi do owrzodzeń i gojenia przez ziarninowanie. Reakcja tkanki na uciśnięcie tętniczki przez wypełniacz jest zwykle odroczona w czasie. Zamknięcie żyły wypełniaczem (podanie bezpośrednie do światła lub ucisk) charakteryzują się wystąpieniem objawów znacznie później, takich jak: przedłużający się ból, obrzęk, zaczerwienienie skóry [32, 45–47]. Utrata widzenia jest najcięższym i najbardziej przerażającym objawem niepożądanym będącym efektem przypadkowego podania pod dużym ciśnieniem wypełniacza do tętnic odgałęziających się od tętnicy szyjnej zewnętrznej (tętnic nadbloczkowej, nadoczodołowej, kątowej oraz grzbietowej nosa) i w konsekwencji zatoru tętnicy ocznej.

W przypadku, gdy wypełniacz podawany jest pod dużym ciśnieniem przez dłuższy czas materiał może dostać się do tętnicy szyjnej wewnętrznej, co skutkować może deficytem krążenia mózgowego lub nawet porażeniem połowiczym [32, 45, 48–50].

WNIOSKI

Celem Rekomendacji PTMEiAA jest poprawa bezpieczeństwa pacjentów, standaryzacja procedur wykonywanych w medycynie estetycznej oraz zdefiniowanie minimalnych wymagań jakościowych podczas wykonywania poszczególnych zabiegów.

Dokładna znajomość anatomii umożliwia bezpieczne wykonywanie zabiegów mających na celu odbudowę utraconej objętości tkanek twarzy.

Zabieg powinien zostać wykonany w miejscu spełniającym wymogi ustawy o działalności leczniczej.

Technika wykonania zabiegu powinna uwzględniać przede wszystkim bezpieczeństwo pacjenta, być dostosowana do doświadczenia i poziomu wyszkolenia osoby wykonującej zabieg.

Postępowanie po zabiegu jest istotne dla uzyskanie optymalnych efektów.

Najczęściej w wyniku iniekcji występuje miejscowy obrzęk, ból czy podbiegnięcia krwawe, zwykle szybko ustępujące. Należy posiadać wiedzę w zakresie leczenia powikłań naczyniowych, które wymagają natychmiastowego włączenia terapii.

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INTERNATIONAL PUBLIC HEALTH CONFERENCE
«PUBLIC HEALTH IN UKRAINE – MODERN CHALLENGES AND DEVELOPING PROSPECTS»
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Dear colleagues!

According to approved "Register of congresses, symposia, scientific-practical conferences and plenums for 2020" by Ministry of Education of Ukraine and Ukrainian Institute of Scientific and Technical Expertise and Information, Sumy State University media supported by medical scientific journal ***Wiadomości Lekarskie*** *(Warsaw, Poland)* will hold international conference «**Public health in Ukraine – modern challenges and developing prospects**», which will take place **23-24 April 2020** on the base of the Medical Institute of Sumy State University (Sumy).

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1. Global health directions. How are health policies` approaches changing?
2. Health economics: why investment in human and country health is profitable.
3. Interdisciplinary and cross-sectoral partnership in public health.
4. Law and ethical principles of public health.
5. Infectious and non-communicable diseases, their impact on population health state.

Conference forms of participation:

- Articles publication
- Theses publication

Publication form: in professional journal ***Wiadomości Lekarskie*** – *Warsaw, Poland* ***(*****Pubmed/ Medline, Scopus, Ebsco, Index Copernicus*****)*** (articles, theses), official publication of Polish Medical Association, incessantly published from 1928.
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