ORIGINAL ARTICLE

THE COMPREHENSIVE EVALUATION OF PATIENTS' CONDITION IN RECOVERY AND RESIDUAL PERIODS OF ANEURYSMAL SUBARACHNOID HEMORRHAGE

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ABSTRACT

The aim: is to evaluate peculiarities of clinical and neurological characteristics, quality of life, brain morphometry changes and metabolic deviations of patients, who suffered from aneurysmal subarachnoid hemorrhage.

Materials and methods: In the period of 2016-2019 we examined 114 patients, who signed the informed consent, taking into account their age, clinical and anatomical form of hemorrhage, disease duration, Hunt-Hess severity grade, complications of acute period. Such parameters were evaluated, as clinical and neurological characteristics, the degree of the Barthel index and the modified Rankin scale, cognitive functioning (MoCA), psycho-emotional sphere and quality of life (HADS, SF-36), morphometric parameters based on brain computed tomography measurements, explored the indicators of apoptosis, mitochondrial dysfunction, intracellular oxidative stress.

Results: Cephalgia (90,35 %), pyramidal syndrome (53,50 %), sensibility deficit (36,84 %) were leading among the all neurological syndromes. Slight dependence and disability grade was found during assessment of the Barthel index and the modified Rankin scale. In 85,96 % of patiens we revealed cognitive impairment of different severity grades. The anxiety was manifested in 65,79 %, depression – in 64,91 % of patients. Due to the morphometry data, the process of cerebral atrophy was detected (central – in 26,31 % of patients, cortical – in 16,67% and mixed – in 28,07 %). AnV+ and PI+ – cells level exceeded normal values in 2,88 and 1,96 times while the level of JC-1+ and ROS+-cells – in 2,17 and 2,82 times ($p<0,01$).

Conclusions: Having studied clinical and neurological, neuropsychological, morphometric and metabolic factors, we found their pathogenetic role in the course of late recovery and residual periods of aneurysmal subarachnoid hemorrhage, that would help us to improve the diagnostic tactics and reveal the predictors of unfavorable outcome.

KEY WORDS: aneurysm, subarachnoid hemorrhage, cognitive impairment, cerebral atrophy, apoptosis

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INTRODUCTION

Among the total number of strokes, hemorrhagic itself accounts for 20%, including 10% of subarachnoid haemorrhage. The most common cause of subarachnoid haemorrhage is the rupture of cerebral saccular aneurysm [1; 2.] The incidence of aneurysmal subarachnoid haemorhage (aSAH) slightly varies in different countries, occuring at a rate of 10-15 cases in 100,000 population per year [3].

The main features of haemorrhage depend on the anatomical location of the aneurysm and due to the number and zones of spilled blood will manifest as a certain pathomorphological cascade: the growth of aseptic inflammation, hypoperfusion, reduction of cerebral metabolism, edema, impaired cerebrospinal fluid circulation and homeostasis with subsequent angiospasm and appearance of secondary complications [4;5;6].

The course of each phase of the pathogenesis, as well as timely surgical intervention, will determine the patient's final outcome, which is favorable among only one third of patients due to findings of certain investigators. Other scientists strongly believe, that in majority of patients it is possible to achieve excellent treatment results (0-1 points on the Rankin scale), but in the case of absence of bleeding into brain parenchyma and ischemic complications. [8].

Functional independence of patients, who suffered from aSAH, should be evaluated in a comprehensive manner, taking into account not only the scales of disability, assesment of cognitive functioning, quality of life and changes in the psycho-emotional sphere, but also considering the analyzed data of brain structural changes and indicators of metabolic disorders. That's why it is advisable to establish correlations between patient's clinical and paraclinical characteristics in order to clarify their role in the pathogenesis of aSAH outcomes [9-21].

THE AIM

The aim: is to evaluate peculiarities of clinical and neurological characteristics, quality of life, brain morphometry changes and metabolic deviations in patients, who suffered from aneurysmal subarachnoid hemorrhage.

MATERIALS AND METHODS

In the period of 2016-2019, having previously signed the informative agreement, we examined 114 patients in the late recovery and residual periods of aneurysmal subarach-

noid hemorrhage, who were undergoing treatment in the Ternopil regional psychoneurological hospital. The study was carried out in accordance with the Helsinki Declaration and was approved by the university ethics commission.The percentage of men was – 64,91 % and of women – 35,09 %. Age distribution of patients was as follows: young age (18-44 years) – 37,72% of patients, middle age (45-59 years) – 62,28%. According to the clinic and anatomical type of hemorrhage we observed: subarachnoid hemorrhage (SAH) – in 45,61% of patients, subarachnoid-parenchymal (SP) – in 26,32%, subarachnoid-ventricular (SV) – in 18,42%, subarachnoid haemorrhage accompanied by parenchymal and ventricular bleeding (SPV) – in 9,65%. We divided patients into 4 groups by the disease duration: 6-12 months – 25,44%, 1-5 years – 32,46%, 6-10 – 27,19% and more than 10 years – 14,91% of patients. The hemorrhage severity in the acute period (Hunt-Hess grading scale) was taken into account. Thus, I grade was found in 12,28%, II – in 57,02%, III – in 22,81%, IV – 2,63%, V – 5,26% of patients. Carotid localization of the aneurysm was in 79,82% of cases, vertebrobasilar – in 20,18% of patients. Endovascular coiling was endured by – 56,14% of patients, clipping – by 19,30%, patients. Surgery was not performed in 24,56% of patients. Also we took into account the acute period complications, which were observed in 42,11 % of patients (moderate-severe vasospasm, ischemic stroke, edema, hydrocephaly and recurrent hemorrhage). The control group consisted of 20 healthy people, being corresponded to the age and gender.

All the patients underwent generally accepted clinical and neurological examination. The degree of disability was assessed according to a modified Rankin scale. The daily living activities were assessed by the Bathel index. The evaluation of the cognitive and psycho-emotional sphere was made by means of special neuropsychological scales (MoCA, HADS), the quality of life – by the questionnaire SF-36.

Brain morphometry indices were studied using computed tomography (Asteion 4, Toshiba, Japan). The following parameters were evaluated: width of subarachnoid spaces (SAS), width of right and left lateral ventricles (LV), maximum size of III ventricle (E), size of IV ventricle, bifrontal index (BFI), bicaudate index (BCI), the index of the central part of the lateral ventricle (ICPLV), ventricular index (VI), frontal horn index (FHI), Hackman index (HI), Schlattenbrandt-Nuremberg index (SNI), Evans ratio (ER).

The study of apoptosis, mitochondrial dysfunction, intracellular oxidative stress was performed by cytofluorimetric method using Epics XL flow cytofluorimeter («Beckman Coulter», USA). The number of peripheral blood leukocytes in the stage of apoptosis (ANV^+-cells) and necrosis (PI^+- cells) was determined using FITC-labeled annexin V reagents from the ANNEXIN V FITC reagent kit («Beckman Coulter», USA). The number of leukocytes with reduced levels of mitochondrial transmembrane potential ($JC\text{-}1^+$ – cells) was determined using the MitoScreen kit («BD Pharmigen», USA). The number of peripheral blood leukocyte with elevated intracellular reactive oxygen species (ROS^+ – cells) was determined using dichlorofluorescein diacetate (DCF-DA) («Sigma Aldrich», USA).

The obtained parameters were expressed as a percentage of the number of all leukocytes. The results of the study were processed using Microsoft Excel 2011 and the computerized system for statistical analysis and data processing Statistica 10.

RESULTS AND DISCUSSION

The most common complaints of the surveyed patients were: headache – in 88,59% of patients, impaired memory and attention – in 65,78% and dizziness – in 48,24%. Less frequently, patients reported fluctuations in blood pressure – 39,47%, headache attacks with nausea and vomiting – 35,08%, limb weakness – 27,19% and sensitivity disorders – 27,19%, stiffness – 19,29%, reduced vision – 14,03%. Seizures were reported in 8,77% of patients.

The value of the Barthel index was (94,73 ± 1,10) points, which corresponded to a slight degree of dependence, Rankin scale – (1,87 ± 0,07) points, which can also be equated with a slight degree of disability.

While analyzing the distribution of disability degrees among patients (Rankin scale), the prevalence of the 3rd (45,45%) and the presence of 4th (9,09%) degree was in patients with more severe type of hemorrhage – subarachnoid haemorrhage accompanied by parenchymal and ventricular bleeding, in contrast to patients with the other type of hemorrhage. It should be noted that patients who hadn't any complications in the acute period mostly received 1st level of disability (43,93%),while 4th and 5th degrees were observed only in the group with the presence of complications. According to the Barthel Index Scoring, the majority of patients (70,17%) were completely independent in all activities of daily living, and the percentage of persons with moderate dependence was 21,93%. The number of patients with moderate dependence was predominant in the group with subarachnoid haemorrhage accompanied by parenchymal and ventricular bleeding – 45,45%, and the highest percentage of completely independent ones was noted in the group with subarachnoid hemorrhage (82,70%). Among the non-operated patients, the number of people with moderate dependence was the highest – 32,14%, unlike those who underwent surgery (in endovascular – 18,75%, in clipping – 18,19%). The number of patients with moderate dependence was predominant in the group with the III degree of severity (by Hunt-Hess scale) – 42,00%, and the severe dependence was found only in those patients who had V severity degree by the Hunt-Hess scale – 16,67%.

The average MoCA score in the general group was (21,71 ± 0,37) points, that corresponded to a moderate cognitive decline. Generally, cognitive disorders of different severity levels were found in 85,96% of patients: mild cognitive decline in 43,86%, moderate – in 23,69%, dementia – in 18,42% of patients. Of all the MoCA subscales, significant changes were found in functions of visual and constructive skills, language, memory and attention. There were inverse

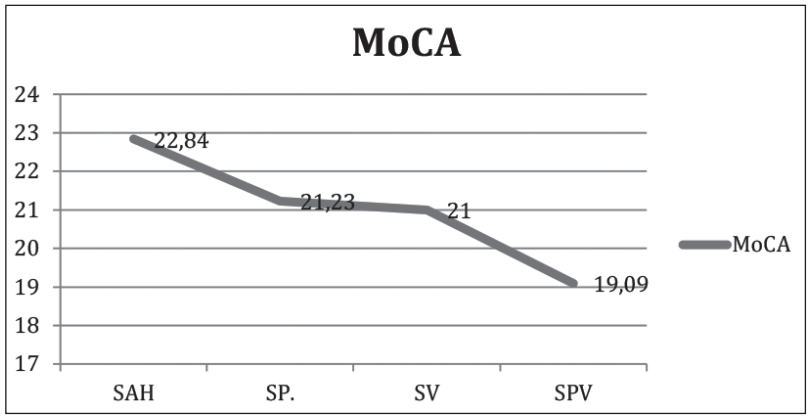

Figure 1. Distribution of results of MoCA scale among patients with different clinical and anatomical form of hemorrhage, points.

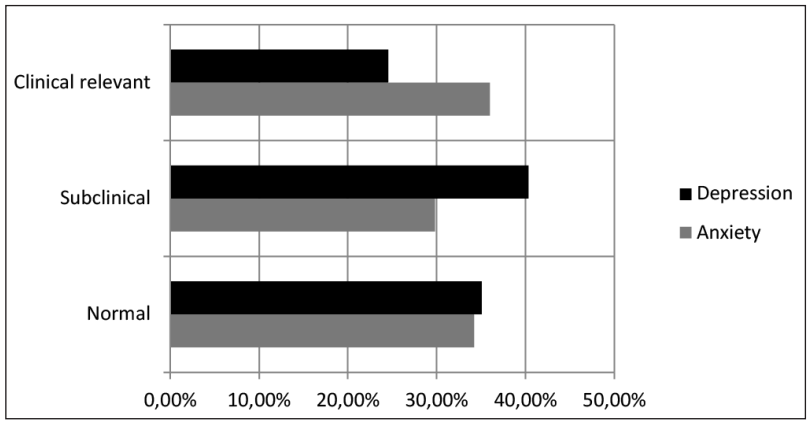

Figure 2. Distribution of patients by level of anxiety and depression (HADS,%).

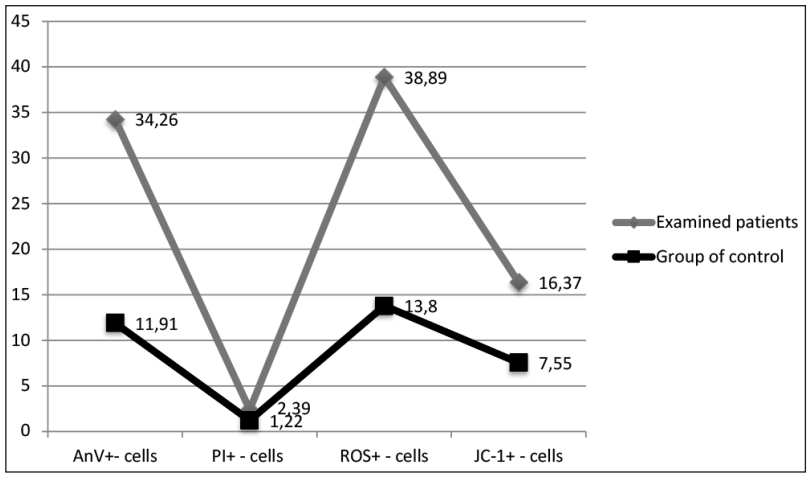

Figure 3. The level of of PI + - cells, AnV+ - cells, JC-1+ - cells and ROS + - cells in the total sample, %.

correlations between the MoCA scale and depression (r = -0,325; p = 0,000) and the Hunt Hess severity (r = -0,310; p = 0,001), as well as the direct correlation with the Barthel index (r = 0,305; p = 0,001). Representatives of the older age group showed lower scores in more subscales than young ones, but statistical significance was observed only in the "name" subscale (p <0,05). The following correlations were obtained in middle-aged patients: MoCA / hemorrhage type – (r = -0,358, p = 0,002), MoCA / Hunt-Hess score (r = -0,434, p = 0,000).

The result of the MoCA test was the lowest in the group of patients with subarachnoid haemorrhage accompanied by parenchymal and ventricular bleeding, but this difference was only significant in comparison with the group of patients who suffered from subarachnoid type of hemorrhage (p<0,01) (Fig. 1). Among the patients with subarachnoid haemorrhage accompanied by parenchymal and ventricular bleeding there was a correlation between the MoCA test result and the Rankin disability level (r = -0,653; p = 0,029). Among patients with the IIIrd Hunt-Hess scale severity degree it was found the correlation between the MoCA test results and the type of hemorrhage – (r = -0,405; p = 0,040).

By using the linear regression method we created a mathematical model that reflects the dependence of cognitive functioning in the residual period of aSAH on such parameters of the acute period, such as the Glasgow Coma Scale score, the severity of the patient's

condition by the Hunt-Hess scale, (I-V), clinical and anatomical form of bleeding (numbered: SAH-1, SP-2, SV-3, SPV-4) and also took into account patients' age. This makes it possible to predict the further cognitive dysfunction during the acute period of the disease. MoCA test score = 28,136 + (- 2,464 * age) + (0,106 * Glasgow Coma Scale score) + (- 0,728 * hemorrhage type) + (- 1,064 * Hunt-Hess score). While analyzing the neuropsychological scale (HADS) data, it was found that the level of anxiety was (9,50 ± 0,36) points and depression – (8,38 ± 0,36) points that corresponded to the level of subclinical manifestations of these psycho-emotional disorders. The structure of patients' anxiety and depression levels is presented in Figure 2. Generally, 65,79% of patients suffered from anxiety and 64,91% had depression. As it was mentioned above, depression negatively affected the MoCA test result. Patients with a higher level of cognitive functioning may also be more critical of their disease and more likely to be depressed.

The significant difference was observed in age groups: anxiety values were (9,65 ± 0,56) points in young people and for the depression was (7,81 ± 0,55) points, while in the middle age group anxiety and depression scored (9,42 ± 0,48) points and (8,73 ± 0,46) points (p <0,01).

While analyzing the results of the SF-36 scale, the following subscale scores were obtained: physical functioning (PF) – (53,30 ± 2,23) points against (68,00 ± 3,68) in the control group (p> 0,05) , physical role functioning (RP) – (16,25 ± 2,51) scores against (72,75 ± 4,87) (p <0,01), bodily pain (BP) – (48,26 ± 1, 75) scores against (72,20 ± 4,40) (p <0,05), general health (GH) – (42,91 ± 1,39) points against (75,90 ± 2,69) (p <0,05), vital activity (VT) – (41,49 ± 1,68) scores against (67,50 ± 2,44) (p> 0,05), social functioning (SF) – (60, 32 ± 1,90 points against (80,12 ± 3,84) (p> 0,05), emotional role functioning (RE) – (24,91 ± 3,06) against (80,00 ± 7, 41) scores (p <0,05), mental health (MH) – (52,59 ± 1,57) points against (62,45 ± 2,67) (p <0,05). Thus, a significant quality of life decrease was observed in all subscales except physical functioning, vital activity and social functioning.

Computed tomography method followed by analysis of morphometric parameters revealed the presence and prevalence of cerebral atrophy. Analyzing the sizes of SAS and IIIrd ventricle, the following types of cerebral atrophy were diagnosed: external – in 16,67%, internal – in 26, 31%, mixed – in 28,07% of patients. Morphometric indices were as follows: width of right lateral ventricle – (0,90 ± 0,03) cm vs (0,56 ± 0,02) cm in control group (p <0,05), left lateral ventricle – (0,92 ± 0,03 cm against (0,57 ± 0,02) cm (p <0,01), maximum width of the 3rd ventricle – (0,71 ± 0,02) cm against (0,34 ± 0,01)) cm (p <0,01), ICPLV – (8,78 ± 0,24) cm vs (10,15 ± 0,44) cm, width of IV ventricle – (1,30 ± 0,02) cm vs (0,88 ± 0,02 cm (p <0,01), BFI – (0,33 ± 0,00) cm vs (0,26 ± 0,00) cm (p <0,01), BCI – (0,14 ± 0,00) cm vs (0,11 ± 0,00), VI – (0,49 ± 0,00) cm vs (0,49 ± 0,01), FHI – (0,56 ± 0,00) cm against (0,44 ± 0,01) (p <0,01), HI – (2,10 ± 0,04) cm against (2,08 ± 0,08), SNI – (24.31 ± 0,93) cm vs (41,77 ± 1,95) (p <0,01), SAS (frontal lobe) – (0,31 ± 0,00) cm against – (0,16 ± 0,02) (p <0,01), SAS (sylvian fissure) – (0,33 ± 0,02) cm against (0,17 ± 0,02) (p <0,01), ER – (0,29 ± 0,00) cm vs (0,24 ± 0,00) (p <0,01).

Significant enlargement of the ventricular system was found in the examined patients: right and left lateral ventricles – in 1,6 times, III – in 2,08 and IV – in 1,47. The expansion of SAS near the frontal lobe was in 1,93 times, and at the sylvian fissure – in 1,94 times. While analyzing the SAS sizing, we detected diffuse atrophy in 29,82% of cases, focal – in 14,03%. Besides, such correlations were calculated, as age/ right lateral ventricle – (r = 0,334; p = 0,000), age/ E (III ventricle) – (r = 0,335; p = 0,000). There were noticed the correlations between the right and left lateral ventricles sizes with the MoCA-test results (r = -0,380; p = 0,000) and (r = -0,479; p = 0,000). Also, statistically significant correlations were obtained between the MoCA test result and morphometric ratios such as BFI, BCI, and Evans index (r = -0,377; p = 0,000), (r = -0,340; p = 0,000), (r = – 0,347; p = 0,000).

According to the methods described above, we explored the content of leukocytes in the stage of necrosis (PI^+ – cells) and apoptosis (AnV^+ – cells), determined the number of peripheral blood leukocytes with elevated content of intracellular reactive oxygen species (ROS^+ – cells). Along with that, we studied the number of leukocytes with reduced levels of mitochondrial transmembrane potential ($JC\text{-}1^+$ – cells).

In the surveyed patients we obtained the increased content of AnV^+ and PI^+ – cells, which significantly exceeded the control group levels – in 2,88 and 1,96 times (p <0,01). The number of $JC\text{-}1^+$ – cells increased in 2,17 times and ROS^+ – cells – in 2,82 (p <0,01) (Fig. 3). The following correlations were calculated: AnV^+ – cells / type of hemorrhage – (r = – 0,297, p = 0,007), $JC\text{-}1^+$ – cells / type of hemorrhage – (r = -0,240, p = 0,038), ROS^+ – cells / AnV^+ – cells – (r = 0,826, p = 0,000) and ROS^+ – cells / PI^+ – cells – (r = 0,515, p = 0,000), $JC\text{-}1^+$ – cells / ROS^+ – cells – (r = 0,659, p = 0,000). The opening of mitochondrial megachannels leads to the release of ROS and the occurence of mitochondrial dysfunction. The correlation obtained between the level of $JC\text{-}1^+$ – cells and AnV^+ – cells – (r = 0,612, p = 0,000) and $JC\text{-}1^+$ – cells and PI^+ – cells – (r = 0,594, p = 0,000) confirms the fact of the inextricable link between apoptotic and necrotic cell death and mitochondrial dysfunction. The inverse correlation between the number of AnV^+- cells and the duration of the disease (r = -0,246, p = 0,033) was obtained, as well as the direct correlation between the level of PI^+ – cells and the size of the SAS at the level of the frontal lobe (r = 0,229, p = 0,047) and at the level of sylvian fissure (r=0,280, p=0,015).

Thus, we studied the features of clinical and neurological characteristics, investigated the quality of life of patients, the structural-morphometric changes of the brain, as well as metabolic disorders in this category of patients. It should be noted that this study reveals key factors that have a disabling effect on a patient's daily activities. In the future, we should study the state of cerebral hemodynamics in the examined patients with the aim of improving the diagnostic tactics, and at the same time it will contribute to a more rational treatment of patients with this pathology.

CONCLUSIONS

Due to the study of clinical and neurological, neuropsychological, structural and morphometric, metabolic factors, we found their pathogenetic role in the formation of features of late recovery and residual periods of aSAH that would help us to improve diagnostic tactics and determine the predictors of adverse disease course.

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Conflicts of interest:
Authors declare no conflict of interest.

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