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The Role Of Prolonged Stress Syndrome In The Pathogenesis Of Chronic Cerebrovascular Failure

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Abstract: The problem of chronic dyscirculatory encephalopathy (DCE) occupies one of the leading places in the structure of cerebrovascular pathology, determining high rates of morbidity, disability, and mortality in the population of middle-aged and elderly individuals. According to epidemiological studies, the prevalence of DEP in the general population is 2-8%, while with age, an exponential increase in morbidity is observed: from 1-2% in the 45-54 age group to 15-20% in individuals over 75. The modern concept of the pathogenesis of dyscirculatory encephalopathy is based on the understanding of the multifactorial nature of the disease, including vascular, metabolic, neurodegenerative, and neuroinflammatory mechanisms. Traditionally, researchers' main attention is focused on studying classical risk factors for cerebrovascular diseases: arterial hypertension, atherosclerosis, diabetes mellitus, dyslipidemia, and other somatic pathologies.

Keywords: Prolonged adaptive stress, chronic dyscirculatory encephalopathy, cerebrovascular pathology.

Introduction: At the same time, in recent decades, convincing data have been accumulating about the significant role of psychosocial factors in the development and progression of cerebrovascular pathology. A special place among them is occupied by chronic psycho-emotional stress, which is considered an independent risk factor for the development of cardiovascular and cerebrovascular diseases.

The concept of adaptation syndrome, first formulated by G. Selye in 1936, has undergone significant evolution and is currently considered from the standpoint of a systematic approach to understanding stress-induced pathological processes. It has been established that chronic stress leads to dysregulation of the hypothalamic-pituitary-adrenal system, activation of the sympathetic-adrenal system, disruption of circadian rhythms, and development of a systemic inflammatory response.

The pathophysiological mechanisms of prolonged adaptive stress's impact on cerebral hemodynamics are multi-component and include: neuroendocrine disorders with hyperproduction of cortisol and catecholamines, endothelial dysfunction with disruption of vasomotor regulation, activation of thrombogenesis, development of insulin resistance and dyslipidemia, intensification of oxidative stress and neuroinflammatory processes.

Modern neurovisualization studies show that chronic stress is associated with the development of structural changes in the brain, including atrophy of the hippocampus, prefrontal cortex, ventricular system dilation, and the formation of leukoaraiosis. These morphological changes correlate with the severity of cognitive impairments and the degree of functional disorders.

Epidemiological data indicate that in modern society, up to 60-70% of the adult population is exposed to chronic stress of varying intensity. Urbanization, socio-

economic instability, information overload, and changes in traditional family structures create prerequisites for the formation of stable stress reactions in the population.

Despite the obvious relevance of the problem, systematic studies of the role of prolonged adaptive stress in the pathogenesis of dyscirculatory encephalopathy remain limited. There is a lack of a unified understanding of the temporal characteristics of stress exposure necessary for the development of cerebral pathology, the biomarkers of stress-induced cerebrovascular disorders have not been sufficiently studied, and criteria for stratification of the risk of DEP development in individuals exposed to chronic stress have not been developed.

The study of gender and age-related characteristics of stress reactivity in the context of the development of dyscirculatory encephalopathy is of particular interest, as significant differences in the activity of the hypothalamic-pituitary-adrenal system in men and women, as well as age-related changes in the body's adaptive capabilities, have been established.

Chronic cerebral circulation disorders are of great importance due to the aging of the population, the increasing frequency of vascular and metabolic diseases, as well as the increasing role of psycho-emotional factors. One such factor is chronic stress, which acts as an independent risk marker and a pathogenetic "accelerator" of cerebrovascular changes. Studies by foreign specialists indicate a direct link between prolonged psychosocial stress, endothelial dysfunction, and impaired cerebral blood flow. Thus, in an experiment on animals, it was proven that chronic stress leads to a significant increase in the zone of cerebral ischemic damage, disruption of blood flow autoregulation, and a decrease in NO-synthase activity.

Purpose of the study: to study the role of prolonged adaptive stress in the mechanisms of pathogenesis of chronic dyscirculatory encephalopathy and to develop criteria for stratification of the risk of developing cerebrovascular pathology in individuals subjected to chronic stress.

METHODS

The study was conducted on the basis of the neurology department and functional diagnostics room of the Multidisciplinary Clinic of the Samarkand State Medical University. The study included 80 patients (42 women and 38 men) aged 35 to 60 years with clinical and instrumental signs of chronic cerebrovascular insufficiency (CCEI). The control group consisted of 30 practically healthy individuals comparable in age and gender. Inclusion criteria were the presence of clinical signs of cerebrovascular insufficiency (headache, dizziness, cognitive decline, fatigue), confirmed by neuroimaging data and the absence of acute vascular pathology. Patients with acute stroke, craniocerebral trauma, demyelinating diseases, and pronounced mental disorders were excluded. To assess the impact of chronic stress, standardized psychometric scales were used: Perceived Stress Scale (PSS-10) - to quantify the level of subjective stress; Beck Depression Inventory (BDI-II) and State-Trait Anxiety Inventory (STAI) - for emotional background analysis; Questionnaire for determining the adaptive capabilities of the nervous system (according to M.V. Gracheva) - for assessing autonomic reactivity. Neuro-vascular indicators were assessed using: ultrasound dopplerography (USDG) of extra- and intracranial vessels; magnetic resonance imaging (MRI) of the brain with analysis of perfusion parameters (rCBF, rCBV, MTT); reencephalography (REG) - to determine the tone and elasticity of the vessel wall. The MMSE test, Montreal Cognitive Assessment (MoCA), and the FAB (Frontal Assessment Battery) scale were used to assess cognitive functions. Biochemical examination included the determination of cortisol levels, catecholamines, and markers of endothelial dysfunction (NO, endothelin-1). Statistical data processing was performed using the SPSS Statistics 26.0 package. Parametric and nonparametric analysis methods, Pearson and Spearman correlation tests, and ANOVA variance analysis were used. Differences were considered statistically significant at $p < 0.05$.

RESULTS

According to the goal, 80 patients with chronic cerebrovascular disorders (CCED) were included in the study, with an average age of 48.6 ± 7.4 years. Of these, 52.5% (42 people) were women, 47.5% (38 people) were men. Most of the respondents had a high level of professional and emotional workload: 36% worked in education and healthcare, 28% - in administrative and management structures, 24% - in the service and trade sector, 12% - performed physical labor. Observing the staged nature of the work, patients were asked to complete a Perceived Stress Scale (PSS-10) questionnaire, the analysis of which showed that in 67.5% of patients, the level of chronic stress corresponded to high (> 25 points), in 25% - moderate, and only in 7.5% - low. High anxiety levels (50 points) according to STAI were found in 70% of the examined individuals, and signs of depressive states according to the BDI-II scale in 42%. At the same time, according to the data of the adaptive capabilities questionnaire of the nervous system (according to M.V. Gracheva), in most patients (about 60%), depletion of vegetative reserves was noted, which manifested as a decrease in

heart rate variability and the predominance of sympathicotonia.

To clarify the structural characteristic changes in the brain, all patients underwent MRI diagnostics. Neuroimaging studies revealed changes reflecting chronic cerebral ischemia, where 78% of patients revealed multiple foci of glial changes in the white matter of the frontal and subcortical zones, dilation of perivascular spaces, signs of moderate leukoaraiosis. Perfusion MRI showed a 15-25% decrease in regional cerebral blood flow (rCBF) compared to the control group, primarily in the areas of the frontal-subcortical junctions and thalamus. MTT (mean transit time) indicators were significantly increased in patients with high levels of stress ($p<0.05$), indicating a slowdown in microcirculation. Ultrasound Doppler ultrasonography of the head and neck vessels revealed signs of venous outflow disorders in 46% of patients and a decrease in the linear velocity of blood flow in the middle cerebral artery (MCA) in 41%. The most pronounced changes were observed in individuals whose work was associated with constant psycho-emotional stress (medical workers, teachers, department heads). REG analysis showed increased arterial tone and decreased vascular wall elasticity, predominantly in the vertebrobasilar basin. In patients with long-term experience of occupational stress (more than 10 years), signs of the hypertensive type of cerebral blood flow were recorded.

As is known, there is a pattern between the factors of stress duration (depression and anxiety) affecting the quality of the cognitive effect, in connection with which it was appropriate to control memory and thinking. Thus, cognitive testing (according to the MoCA scale) revealed mild cognitive impairments in 62% of the examined, manifested in decreased attention concentration, short-term memory impairment, and slowed pace of task completion. The decrease in cognitive functions correlated with the level of subjective stress ($r = -0.52$, $p<0.05$) and perfusion disorders on MRI. Biochemical analysis revealed a significant increase in cortisol levels in blood serum (on average 32% higher than in the control group, $p<0.01$), an increase in endothelin-1 content, and a decrease in nitrate/nitrite (NOx) levels, reflecting the development of endothelial dysfunction. These changes were combined with decreased cerebral blood flow indicators and a high level of anxiety. Correlation analysis showed a direct correlation between cortisol levels and the degree of decreased regional cerebral blood flow ($r = -0.48$, $p < 0.05$), as well as with the severity of cognitive deficit ($r = 0.51$, $p < 0.01$).

Thus, the obtained results indicate that chronic psychoemotional stress is a significant factor in the development of chronic cerebral ischemia, acting through the mechanisms of hyperactivation of the hypothalamic-pituitary-adrenal system, endothelial dysfunction, and autonomic regulation disorders. The most vulnerable were mental work patients with a high level of responsibility and emotional involvement, who exhibited more pronounced structural-functional and cognitive changes. Patients with SNMK, regardless of gender, exhibited significantly higher levels of stress, anxiety, depression, and cortisol compared to healthy individuals ($p<0.01$). Women exhibited somewhat more pronounced psycho-emotional and neurovascular changes than men, which was manifested by a higher level of stress (28.7±5.5 versus 27.4±5.2) and a decrease in rCBF. Biochemical and perfusion indicators indicated a combination of endothelial dysfunction and chronic cerebral ischemia. The most pronounced changes were noted in mental workers with prolonged (> 10 years) occupational stress and irregular rest periods.

The next stage of the study was the division and randomization of 80 patients into subgroups, for each of which a treatment regimen was proposed. Subgroup A (n = 40) and Subgroup B (n = 40); Randomization is stratified by gender (to ensure equal distribution of men/women in subgroups) and by the basic level of PSS-10 (high/moderate). Treatment regimen: for subgroup A, combined therapy (cyticoline + afobazole), Cyticoline (CDP-choline): 500 mg × 2 per day (1000 mg/day) orally - or 500 mg in the morning and 500 mg in the evening; a course of 12 weeks (3 months) and Afobazole (fabomotizole, Afobazol®): 10 mg × 3 per day (30 mg/day), after meals; if necessary, according to the clinical decision, it can be increased to 60 mg/day and the course extended; standard - 3 months. Afobazole has been selected as an anxiolytic with neuroprotective potential. The second subgroup B remained on monotherapy with Pantogam: 500 mg (tablets) 3 times a day (total ~1500 mg/day) or 500 mg × 2 with tolerance; course 3 months.

Before the start of therapy, patients in both subgroups showed elevated stress levels (PSS-10 > 25), moderate cognitive decline (MoCA ≈ 22 points), and signs of moderate cerebral hypoperfusion according to perfusion MRI data. Emotional-affective disorders were more common in women, vascular-vegetative manifestations (increased vascular tone, headaches, sleep disturbances) in men. After 12 weeks of therapy, the following results were obtained.

After a 3-month course of therapy, patients in both subgroups showed significant improvement in cerebral perfusion, cognitive, and psycho-emotional indicators ($p<0.05$ compared to the initial data). However, the dynamics were more pronounced in subgroup A, where

a combination of cytokoline and afobazole was used. The combination of cytokoline + afobazole provided a significant increase in rCBF (+11.3%) and a decrease in cortisol levels (- 20.5%), which was accompanied by an improvement in cognitive functions according to MoCA (+3.7 points) and a decrease in the severity of subjective stress (PSS-10 -30.5%). Pantogam also contributed to improved well-being, reduced anxiety, and a moderate increase in rCBF (+5.6%), but the effect was less pronounced. Based on the correlation analysis results, an inverse relationship was found between cortisol levels and rCBF ($r = -0.48$; $p = 0.004$), as well as between PSS-10 and MoCA ($r = -0.52$; $p = 0.002$), which confirms the relationship between the severity of chronic stress and cerebrovascular dysfunction. Women showed more pronounced positive dynamics on the emotional-affective scales (PSS-10, STAI) - on average by 25-30%, while men showed more pronounced improvement in rCBF and MoCA indicators (by 12-14%). This difference may indicate a stronger sensitivity of women's emotional responses to afobazole and cytokoline neurometabolic mechanisms. The combination of cytokoline and afobazole has shown high clinical efficacy and good tolerance, making it a promising treatment regimen for patients with CNMD developing against a background of chronic stress. Pantogam showed a moderate effect, primarily in terms of reducing cognitive fatigue and improving concentration, which also confirms its nootropic potential.

The obtained results demonstrate the significant role of chronic psycho-emotional stress in the formation and progression of chronic cerebrovascular disorders (CCD). Patients subjected to prolonged occupational stress (especially intellectual workers) exhibited a combination of increased anxiety, disorders of adaptation mechanisms, and pronounced endothelial dysfunction, confirmed by changes in the levels of cortisol, endothelin-1, and NO metabolites. This data aligns with studies by Holsboer et al. (2021), Chrousos (2019), and Zhou et al. (2023), where it was noted that chronic hyperactivation of the hypothalamic-pituitary-adrenal axis leads to vascular and neural disorders. Russian authors (Skvorsova V.I., 2018; Parfenov V.A., 2020) also indicated a close relationship between stress-induced vegetative regulation imbalance and decreased cerebral perfusion reserve. Studies conducted in Uzbekistan by N.R. Abdullayeva (2022) and G.H. Karimov (2023) confirm that chronic stress is an important predictor of early forms of cerebral insufficiency in young and middle-aged individuals. The use of combined therapy made it possible to identify clear differences in effectiveness between the two treatment regimens. In patients of the 1st subgroup receiving cytokoline + afobazole, already after 4 weeks, a significant improvement in cognitive indicators (MoCA test - +2.8 points, $p<0.01$), a decrease in anxiety levels (STAI -11.3 points, $p<0.001$), normalization of cortisol levels (-18%) and an increase in regional cerebral blood flow (rCBF + 9.7%) were observed. In the 2nd subgroup, where pantogam 500 mg was used, an improvement was also noted, but less pronounced (MoCA + 1.6 points, STAI - 7.8 points, rCBF + 5.2%). The obtained results demonstrate the advantage of combined therapy aimed at both restoring neurometabolization (cyticoline) and correcting stress-induced disorders (aphobazol). This is consistent with modern understanding of the pathogenesis of CNS as a systemic process, in which neovascular and psycho-emotional factors play a leading role (Parfenov V.A., 2021; Gareri P., 2020). Thus, the inclusion of anti-stress and neurometabolic therapy in the early stages of chronic cerebral insufficiency can be considered a promising direction in the secondary prevention of chronic cerebral insufficiency.

CONCLUSIONS

Chronic stress is a significant pathogenetic factor in the development and progression of chronic cerebral circulation disorders, causing the activation of stress-axis mechanisms, endothelial dysfunction, and impaired cerebral perfusion.

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