IJIMM, Volume 3, Issue 2, 2025 ISSN: 2995-5319
http://medicaljournals.eu/index.php/IJIMM/issue/view/3

INTERNATIONAL JOURNAL OF INTEGRATIVE AND MODERN MEDICINE

Chronic Cerebral Ischemia: From Pathogenesis to Therapy

G. T. Madjidova
Samarkand State Medical University 2nd Department of Internal Medicine and Cardiology, Senior Lecturer

N. T. Umarova., O. S. Nekbaeva., Bobomuradov G. A.
Doctor's office, Samarkand branch of the Republican Scientific Center for Urgent Ambulance, Samarkand Uzbekistan

Annotation: Currently, there is an increase in the prevalence of cerebrovascular diseases, which significantly reduce the quality of life and often lead to disability of patients. Diseases of small-caliber cerebral vessels account for about 40% of dementias in the world and a fifth of strokes that occur throughout the year worldwide. Structural damage to the brain associated with cerebral microangiopathy (diffuse white matter lesions, multiple lacunar infarctions, microbleeds, secondary cerebral atrophy) can remain clinically unnoticeable for a long time, but significantly increase the risk of dementia and disabling strokes. The main etiopathogenetic factor of cerebral microangiopathy is arterial hypertension, causing arteriosclerosis of small penetrating arteries and arterioles. The most important initiating link in this process is endothelial dysfunction. Available data indicate an increase in circulating markers of endothelial damage in patients with cerebral microangiopathy. Timely complex therapy is a decisive factor in the reverse development of endothelial dysfunction and reliable prevention of cerebrovascular disease. The drug Divaza, which has pleiotropic effects, is a pathogenetically substantiated adjuvant drug for the treatment of anxiety-depressive symptoms associated with cerebral microangiopathy.

Keywords: cerebrovascular disease, cerebral microangiopathy, arterial hypertension, endothelial dysfunction, Divasa.

Introduction

In recent years, there has been an increase in the prevalence of cerebrovascular diseases worldwide, significantly reducing the quality of life and often leading to disability of patients. In the structure of cerebrovascular disease, ischemic brain damage occupies a dominant position and is represented by two main syndromes: cerebral infarction associated with pathology of large extra- and intracranial arteries or cardiogenic embolism, and cerebral microangiopathy (damage to penetrating arteries of small and medium caliber - cerebrovascular insufficiency). Cerebral microangiopathy is less dramatic than acute cerebrovascular accident, but gradually leads to significant losses in the quality of life of the elderly population. Small-caliber cerebrovascular disease accounts for about 40% of dementias in the world [1] and a fifth of strokes that occur throughout the year worldwide . Strokes associated with cerebral microangiopathy (or lacunar) are not severe, and most patients survive and remain physically independent, but in 36% of cases they subsequently have cognitive impairment of varying degrees . Structural damage to the brain associated with cerebral microangiopathy (diffuse white matter lesions, multiple lacunar infarcts, microbleeds, secondary cerebral atrophy) may remain clinically unnoticeable for a long time, but significantly increase the risk of dementia and disabling strokes . Therefore, special attention is paid to the issues of treatment, prevention or slowing the progression of vascular pathology of the brain and, most importantly, improving the quality of life of this category of patients. First of all, high-quality treatment is associated with early diagnosis of small cerebral vessel disease, which requires good knowledge by clinicians of the initial symptoms of the clinical manifestation of the disease.

Clinical manifestation of chronic cerebral ischemia

The clinician should be alerted by the presence of mild cognitive deficit in the patient. Typically, this is a disorder of regulatory cognitive functions and attention with full preservation of everyday independence and professional skills. The combination of impaired concentration with mild or moderate symptoms of anxiety and depressive nature and barely noticeable changes in gait in the form of slowing down, shortening of the step, instability (complaints of dizziness) may indicate the clinical debut of vascular encephalopathy. These symptoms may be an indication for magnetic resonance imaging (MRI) of the brain, which is usually not required in routine practice. MRI helps to verify various variants of morphological changes associated with the pathology of small cerebral arteries, the main ones of which are diffuse white matter damage (leukoencephalopathy), lacunar infarctions, microhemorrhages, secondary cerebral atrophy.

The earliest clinical marker of cerebral perfusion insufficiency is anxiety-depressive disorders, mainly of an asthenic nature, behind the façade of which mild cognitive impairment is hidden. Anxiety-depressive symptoms associated with cerebral microangiopathy are often described as difficult to diagnose and difficult to treat.[2] Difficulties in diagnosing depression in the elderly are primarily associated with the peculiarities of the clinical picture of depression and the fact that this category of patients predominantly seeks medical attention from general practitioners who lack the skills and experience in assessing mental status.

Peculiarities of the clinical picture of depression in elderly patients: prevalence of somatic symptoms of depression over mental symptoms; severe impairment of vital functions, especially sleep; anxiety, irritability, and grumpiness, which are often considered by others to be features of old age, can mask mental symptoms of depression; cognitive symptoms of depression are often assessed within the framework of senile forgetfulness or initial manifestations of dementia; significant fluctuations in symptoms; incomplete compliance with the criteria for a depressive episode (individual symptoms of depression); close connection between exacerbations of a somatic disease and depression; presence of common symptoms of depression and a somatic disease. The expanded clinical picture of cerebral microangiopathy is characterized by clinically significant cognitive decline corresponding to a moderate cognitive disorder. Additionally, the patient may have clinically significant depression, moderate frontal dysbasia or postural instability, clear pseudobulbar manifestations in the form of dysarthria and emotional disinhibition.[3] Everyday activity may be limited mainly due to its most complex, instrumental types.

Diagnosis of cerebral microangiopathy

First of all, the doctor should not neglect the patient's active complaint of forgetfulness. It is necessary to analyze how the patient's forgetfulness affects his daily functioning. It is also important to obtain objective evidence from relatives about the patient's recent excessive forgetfulness. For example, that the patient cannot remember new names, has difficulty counting. Moderate cognitive impairment is characterized by constant forgetfulness, fatigue when performing normal mental work. The described disorders cause difficulties for the patient, but do not deprive him of independence. Such a patient cannot properly organize his activities, gets tired quickly, often makes mistakes due to inattention. When talking with the patient, the doctor may notice that the patient has difficulty independently stating the anamnesis, does not understand the doctor's recommendations. If such a patient is seen by a doctor with an accompanying relative, then when trying to answer the doctor's question, he turns to the accompanying relative for support or a hint. This phenomenon is called the "symptom of turning head". A multitude of non-specific complaints in an elderly patient should also alert the clinician, especially if the patient cannot explain their essence. Having assumed a cognitive deficit in the patient's anamnesis, the doctor should identify and weigh the risk factors for vascular cognitive impairment: arterial hypertension of unknown duration, past excess weight, cardiac pathology, impaired glycemic control, etc. Vascular cognitive impairment is necessarily accompanied by disturbances in the neurological status, in particular, gait is almost always impaired. Gait disturbances can be easily seen even by a doctor who does not have the skills of neurological examination.[4] The

patient's gait becomes slow, he experiences difficulties in starting to walk, turning, shuffles, falls are possible, actively complains of instability. In general, the gait resembles careful walking.

Diagnostic search in the presence of cognitive impairment includes two main stages. At the first stage, syndromic diagnostics are carried out.

Syndromic diagnostics reveals a decrease in cognitive abilities compared to the individual norm and assesses the severity of cognitive impairment. Neuropsychological tests can be of considerable assistance in syndromic diagnostics. The easy-to-use Mini - Cog test is used for screening assessment of the cognitive sphere. The most sensitive and specific to moderate cognitive impairment is the Montreal Cognitive Assessment Scale (MoCa), which includes a study of various cognitive spheres: attention span, executive functions, memory, speech, visual-constructive skills, abstract thinking, counting and orientation.

At the second stage of the diagnostic search, the most probable cause of cognitive impairment is determined, i.e. nosological diagnostics is carried out. The results of neuroimaging are of great importance for verification of the vascular nature of cognitive impairment . In accordance with modern requirements, the diagnosis of vascular cognitive impairment is not valid in the absence of neuroimaging confirmation.

Further progression of the disease in some patients may lead to the development of dementia with limitations of basic types of daily activities and dependence on outside help. Progression of motor disorders (walking and balance) often leads to falls, which significantly limit the patient's mobility.[5] The burden of vascular dementia for the patient, his environment and society as a whole is an important factor prompting the physician to early diagnosis and treatment of cerebral microangiopathy.

Pathogenesis of cerebral microangiopathy

An absolute requirement for adequate treatment of cerebral microangiopathy symptoms is not only symptomatic but also pathogenetic therapy. The latter should motivate the clinician to understand the basics of the pathogenesis of chronic cerebral ischemia. The main etiopathogenetic factor of cerebral microangiopathy is arterial hypertension, which causes arteriosclerosis (lipohyalinosis , fibrinoid necrosis or microatheromatosis) of small penetrating arteries and arterioles. Endothelial dysfunction (ED) is the most important initiating link in this process. Most experts consider the disruption of endothelial properties to be the main mechanism of arterial hypertension. Cardiovascular risk factors for chronic cerebral ischemia, such as aging, hyperhomocysteinemia, postmenopause, smoking, diabetes mellitus, hypercholesterolemia, and hypertension, may also initiate or worsen ED.[6] There are currently no specific studies assessing the relationship between peripheral and cerebral vascular endothelial function. However, existing data show an increase in circulating markers of endothelial damage in patients with cerebral microangiopathy. For example, our own study including 262 patients with vascular depressive symptoms showed a relationship between the level of endothelial function biomarkers (endothelin-1, C-reactive protein, monocyte chemoattractant protein, circulating desquamated endothelial cells and fibrinogen) and the level of depression.

Today it is already completely clear that the endothelium is an important homeostatic organ that controls the regulation of vascular tone. Endothelial cells are capable of synthesizing a wide range of anti-atherosclerotic substances, in particular nitric oxide (NO), which is produced as a result of L-arginine metabolism under the influence of endothelial NO synthase (eNOS), synthesized in endothelial cells. At the early stages of endothelial damage, only functional reversible changes in endothelial function occur, which are usually referred to as "endothelial dysfunction".

The fundamental feature of ED is a violation of NO bioavailability and, accordingly, a decrease in vascular dilation in response to endothelial stimuli. Although the exact mechanisms of impaired NO bioavailability in patients with arterial hypertension remain unknown, the most likely is considered to be a violation of the L- arginine pathway of NO synthesis. In addition to disruption of NO-related vasodilation , decreased bioavailability of NO leads to increased leukocyte adhesion, proliferation of vascular muscle cell wall, expression of adhesion molecules, as well as platelet adhesion and

aggregation.[7] Oxidative stress, which causes accumulation of a large number of active oxygen species (free radical compounds) in the blood, significantly stimulates the progression of ED . Even with normal NO synthesis, its very rapid inactivation occurs with severe oxidative stress.

The main consequence of disruption of endothelium-dependent Vasodilation is an increase in peripheral resistance. Arterial rigidity contributes to an increase in pulse pressure, which is a hemodynamic stressor for the brain, since the brain has low resistance to pulse shock flow. Shock pressure primarily damages small-caliber cerebral vessels. Dysfunction of penetrating arteries and arterioles leads to a disorder of the mechanisms of autoregulation of cerebral circulation and a violation of the integrity of the blood-brain barrier [8]. An increase in the permeability of the blood-brain barrier is accompanied by extravasation of plasma components both directly into the arterial wall (which contributes to its thickening and disintegration) and into adjacent areas of the brain with the development of perivascular edema (which may be one of the mechanisms of white matter damage), as well as aseptic inflammation processes. These changes are an important stage preceding brain tissue damage, including stroke (primarily of the lacunar subtype). Due to more unfavorable blood supply conditions, the subcortical and periventricular white matter of the cerebral hemispheres may suffer to a greater extent than the gray matter of the brain, which is the cause of the clinical picture of chronic cerebral ischemia. As a result of damage to small vessels of the brain, perfusion in the frontal subcortical areas of the brain is disrupted. Extensive zones of incomplete infarctions with demyelination , loss of oligodendrocytes and axons appear in the white matter. Recently, studies have accumulated showing a relationship between arterial rigidity and structural changes in the brain: white matter hyperintensity in the T2 mode of MRI (leukariasis), lacunar infarctions and atrophy of the cerebral cortex [9].

Treatment of patients with cerebral microangiopathy

In the early stages of cerebral microangiopathy, treatment is carried out taking into account risk factors, with the aim of preventing or significantly slowing down the progression of the disease, including the development of acute conditions. The main strategies include:

normalization of blood pressure, carbohydrate and lipid metabolism; control of smoking, obesity and physical inactivity; limitation of alcohol, salt, animal fats. To implement these measures, first of all, the patient should be motivated to follow a proper diet rich in antioxidants, increase physical activity. For example, the so-called Mediterranean diet prevents cognitive impairment . Experimental studies have shown that high doses of antioxidant vitamins are extremely effective in restoring normal endothelial function, but intervention studies with the clinical use of these substances (vitamins C and E) could not convincingly confirm this .[10] However, other antioxidants, such as flavonoids contained in red wine and chocolate, have recently demonstrated an improvement in endothelial function in peripheral large arteries . The benefits of chocolate are associated with the polyphenols present in cocoa, which increase the bioavailability of NO and reduce ED.

As antihypertensive drugs, the most justified is the use of angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists, since these drugs increase the reactivity of small cerebral vessels, and also have antioxidant and anti-inflammatory activity . In case of lipid metabolism disorders, statins should be considered . There is convincing evidence that lowering LDL cholesterol increases the endothelium-dependent vasodilation . This is due to the fact that, in addition to reducing blood cholesterol levels, statins have a cholesterol-independent pleiotropic effect, which is based on stabilization of the vascular wall.

Of course, the system of these measures has a positive effect on endothelial function and the NO system, but is not optimal, which suggests a search for more effective agents that affect both the endothelium and clinical symptoms. One of the drugs with a targeted effect on the endothelium is the drug Divaza , which is well known to clinicians and has a whole range of pharmacological effects. Preclinical studies of Divaza were conducted in accordance with national and international recommendations in leading research centers in Russia and abroad. Clinical studies have confirmed a decrease in the level of ED markers against the background of Divaza intake in patients with clinical

manifestations of cerebral microangiopathy. For example, in an open comparative study led by O. V. Kolokolov et al . (2016) showed that against the background of taking Divaza , the levels of the main markers of ED (C-reactive protein, monocyte chemoattractant protein-1, endothelin-1, etc.) statistically significantly decreased, C-reactive protein and monocyte chemoattractant protein-1 reached normal values. In the comparison group, the levels of markers did not change, and the level of endothelin-1 even statistically significantly increased, which indicates the progression of the pathological process . In addition, Divaza has a positive effect on the parameters of the blood coagulation system - fibrinogen and von Willebrand factor .

Large multicenter studies have shown the success of Divaza in relation to the initial clinical symptoms of cerebral microangiopathy. The results confirmed that the use of Divaza leads to an improvement in asthenia, cognitive functions, sleep, quality of life and is safe in the treatment of elderly and senile patients with asthenic and cognitive disorders . The presence of an anxiety-asthenic symptom complex should be considered as the main indication for prescribing Divaza to patients with chronic cerebral ischemia. Taking into account the time of regression of the main symptoms and the increase in patient activity, the course of treatment with Divaza is 8-12 weeks.

Conclusion

Endothelial dysfunction associated with arterial hypertension can be considered as an initiating pathogenetic link in the development of cerebral microangiopathy. At the early stages of endothelial damage, reversible functional changes in endothelial function occur, which is an important motivating factor for early diagnosis of initial clinical manifestations of cerebral microangiopathy and targeted therapy of the endothelium. The success of treatment in each specific case depends on the correct correction of individual risk factors, primarily optimally selected hypotensive therapy. One of the drugs with a targeted effect on the endothelium is Divaza , which has shown a positive effect on markers of endothelial dysfunction in clinical and laboratory studies. Additional inclusion of Divaza in complex treatment not only improves endothelial function, but also has a positive effect on affective and cognitive symptoms.

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