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PATHOGENETIC INTERRELATIONSHIP OF MATRIX METALLOPROTEINASES AND MONOAMINES IN COMORBID COURSE OF MULTIFOCAL ATHEROSCLEROSIS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

ПАТОГЕНЕТИЧНИЙ ВЗАЄМОЗВ'ЯЗОК МАТРИКСНИХ МЕТАЛОПРОТЕЇНАЗ ТА МОНОАМІНІВ ПРИ КОМОРБІДНОМУ ПЕРЕБІГУ МУЛЬТИФОКАЛЬНОГО АТЕРОСКЛЕРОЗУ ТА ХРОНІЧНОГО ОБСТРУКТИВНОГО ЗАХВОРЮВАННЯ ЛЕГЕНЬ

Motsak T. M.
PhD, Associate Professor,
Associate Professor at the Department internal medicine with gastroenterology course
Bogomolets National Medical University
Kyiv, Ukraine

Моцак Т. М.
доктор філософії, доцент,
доцент кафедри внутрішньої медицини з курсом гастроентерології
Національний медичний університет імені О. О. Богомольця
м. Київ, Україна

Dolynna O. V.
Candidate of Medical Sciences,
Associate Professor,
Associate Professor at the department internal medicine with gastroenterology course
Bogomolets National Medical University
Kyiv, Ukraine

Долинна О. В.
кандидат медичних наук, доцент,
доцент кафедри внутрішньої медицини з курсом гастроентерології
Національний медичний університет імені О. О. Богомольця
м. Київ, Україна

Novyk D. S.
Assistant Professor at the Department internal medicine with gastroenterology course
Bogomolets National Medical University
Kyiv, Ukraine

Новик Д. С.
асистент кафедри внутрішньої медицини з курсом гастроентерології
Національний медичний університет імені О. О. Богомольця
м. Київ, Україна

Introduction and relevance of the topic. Multifocal atherosclerosis (MAS) remains one of the most acute problems of modern medicine [1]. Unlike isolated damage to one vascular area, MAS is characterized by simultaneous involvement of the coronary, cerebral and peripheral basins.

Such a generalized process automatically transfers the patient to a group of high cardiovascular risk [1, 2, 3].

However, clinical reality is often complicated by comorbid conditions, among which chronic obstructive pulmonary disease (COPD) occupies a special place. Both diseases have common risk factors (smoking, age, systemic endothelial dysfunction) and are supported by common mechanisms of progression [4, 5].

The key point in the development of both pathologies is the systemic alteration of connective tissue, regulated by matrix metalloproteinases (MMPs), and the disruption of neurohumoral regulation with the participation of monoamines, such as serotonin and dopamine [6, 7]. Understanding how these markers correlate with each other in conditions of combined pathology is the foundation for predicting critical events, such as myocardial infarction or ischemic stroke. MMPs are a family of zinc-containing endopeptidases responsible for the degradation of extracellular matrix components, with MMP-2 and MMP-9 playing a special role in the context of MAS [6]. MMP-2 is involved in the early stage of plaque formation and stimulates the migration of smooth muscle cells. MMP-9 is synthesized mainly by macrophages in the lipid core of the plaque. Its excessive activity directly leads to thinning of the fibrous cap, making it vulnerable to rupture under the action of hydrodynamic blood pressure.

In concomitant COPD, these same enzymes cause degradation of elastin in the alveoli, which leads to the formation of emphysema and a decrease in the diffusion capacity of the lungs. Thus, a high level of MMPs in the blood is a universal marker of tissue destruction.

Neurotransmitter regulation in MAS and COPD undergoes significant changes due to chronic hypoxia. Serotonin (S): In addition to its functions in the central nervous system (CNS), serotonin is a potent vasoconstrictor and stimulator of platelet aggregation [8]. In pathology, its excess in peripheral blood contributes to angiospasm, worsening perfusion in already stenosed arteries. Dopamine (D): Acts as a marker of the activity of the sympathoadrenal system. Its fluctuations reflect the degree of adaptation of the body to chronic ischemia and hypoxemia [9].

The combination of tissue ischemia and systemic hypoxemia creates a unique biochemical background that accelerates the destabilization of atherosclerotic plaques and leads to a critical decrease in target organ perfusion [1, 2, 10].

The aim of this work is to comprehensively study the relationships between these biomarkers and MMP levels in patients with generalized atherosclerosis and comorbid COPD to identify the most significant predictors of vascular catastrophes.

Materials and methods of the study. To study the above mechanisms, 86 male patients were examined, mean age 67.4±8.5 years. The study design involved a comparative analysis of two groups: Group 1: Patients with MAS, including intermittent claudication syndrome (ICS) (n=42) combined with COPD, Group 2: MAS patients who have a history of acute events (MI or II) without COPD (n=44). Control group (CG): 18 practically healthy individuals comparable in gender and age. Diagnostic complex: Enzyme-linked immunosorbent assay (ELISA): Determination of serum concentrations of MMP-2, MMP-9, serotonin and dopamine. Clinical status assessment: 6-minute walk test (PWD – pain-free distance, MWD – maximum walking distance), Montreal Cognitive Assessment (MoCA). Spirometry: Assessment of external respiratory function for the COPD group.

Results and clinical analysis. The results of the study demonstrated a significant ($p<0.05$) increase in destabilization markers in all groups of patients with MAS compared to CG. MMP-2: In patients of Group 2, the indicators exceeded CG by 58.4% ($p < 0.01$). The highest levels were recorded in patients of Group 1 (MAS+COPD), where the values were 1.6 times higher than the control ($p < 0.001$). MMP-9: The level of this enzyme, which is directly responsible for the risk of thrombosis, was higher by 65.2–66.3% ($p<0.01$) in patients who had already suffered a heart attack or stroke.

Regarding the neurotransmitter profile. A significant increase in serotonin levels ($p<0.001$) and dopamine ($p<0.01$) was found in patients with a generalized process. It is especially interesting that in the group with concomitant COPD, the level of dopamine was stably high, which indicates a state of constant stress of adaptive mechanisms in conditions of respiratory failure.

Correlation with clinical manifestations. The analysis revealed a clear dependence: the higher the level of MMP-9 and serotonin, the shorter the walking distance (severity of intermittent claudication), the lower the score on the MoCA scale (cognitive deficit), the more frequent were episodes of painless myocardial ischemia according to Holter monitoring.

The obtained data confirm that multifocal atherosclerosis is not a local vascular problem. It is a systemic biochemical disorder. The addition of COPD creates a "vicious circle": hypoxia stimulates the release of dopamine and serotonin, which cause vasospasm; at the same time, systemic inflammation activates MMP, which destroys the walls of blood vessels and alveoli.

High levels of MMP-2 and MMP-9 in blood plasma can be considered as a biomarker of atherosclerotic plaque. If these indicators significantly exceed

the norm, the plaque is likely to be vulnerable, even if the stenosis is not critical according to angiography.

Conclusions. Patients with multifocal atherosclerosis are characterized by pronounced activation of matrix metalloproteinases, in particular, MMP-2 and MMP-9, the levels of which are 1.6–1.8 times higher than in healthy individuals ($p < 0.001$). The comorbid course of MAS and COPD is accompanied by the most aggressive biomarker profile, which is due to the combination of ischemic and hypoxic stimuli. Serotonin and dopamine imbalance in such patients correlates with a decrease in exercise tolerance and deterioration of cognitive functions. Determination of MMP and neurotransmitter levels has high diagnostic value for identifying patients with unstable atherosclerosis and needs to be taken into account when developing secondary prevention strategies.

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