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New Concept of Secondary Prevention of Cardiovascular Events in Patients with Multifocal Atherosclerosis Complicated by Chronic Obstructive Pulmonary Disease

Secondary prevention of cardiovascular events, especially in patients with the combined pathology of multifocal atherosclerosis (MAS) and chronic obstructive pulmonary disease (COPD), is a highly relevant topic of modern medicine. Ischaemia of vital organs causes pathologically high release of neurotransmitters, so the search for new strategic approaches that will be able to stabilise this condition is extremely relevant.

Objective — to optimise the levels of serotonin (S), histamine (H) and matrix metalloproteinases (MMP) in patients with MAS and COPD.

Materials and methods. The study included 68 male patients (67.5 ± 3.8) years old with lesions of the cerebral, coronary, and femoral vascular territories, and manifestations of intermittent claudication syndrome. Patients in the MAS-2 group (n = 36) (GOLD 2) had concomitant COPD. Control group (CG) — 18 practically healthy men (65.6 ± 4.2) years old. Examination included: determination of the ankle-brachial index, Doppler ultrasound of the neck arteries and arteries of the lower extremities, spirography, measurement of walking distance, and determination of S, H, MMP-2,and MMP-9 in the blood. Patients of both groups of MAS on the background of basic treatment were prescribed cilostazol (Cil) (50 mg twice a day), *GABA* — aminalon (A) (250 mg twice a day), catechin (C) — *Green T-Max* (1 capsule per day). The course of treatment lasted 16 weeks.

Results and discussion. The initial examination of patients in both groups showed significantly ($p < 0.01$) higher levels of neurotransmitters S, H, and MMP-2 and MMP-9, compared to the CG, 5—7-fold morning peaks of S in blood plasma were recorded. Volumetric blood flow indicators were significantly ($p < 0.01$) lower, compared to the CG. After the treatment, we managed to eliminate the morning 5—7-fold increases of S and avoid the development of serotonin syndrome, as well as improve blood supply in all affected vascular territories, significantly ($p < 0.05$) increased volumetric blood flow, and significantly decreased levels of MMP-2 ($p < 0.001$) and MMP-9 ($p < 0.01$) in peripheral blood. The combination of Cil, A and C significantly ($p < 0.05$) reduces and stabilises the levels of S and H in the blood in both groups of patients. Clinically, this was manifested by an improvement in the function of external respiration and an increase in pain-free walking distance.

Conclusions. The work was based on a new strategic direction of secondary prevention of serious cardiovascular events, based on the correction of disorders of neurotransmitter regulation, namely, S and H. Extremely high levels of S and H were corrected by the use of Cil, A and C, which allowed stabilisation and improvement of the clinical condition of patients with MAS and COPD.

Keywords

Chronic obstructive pulmonary disease, multifocal atherosclerosis, serotonin, histamine, metalloproteases.

Multifocal vascular lesion of atherosclerotic genesis is a very common disease today; however, it remains insufficiently studied. Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality in the world, causing about three million deaths annually [5]. It has been proven that comorbidity with cardiovascular diseases significantly increases the mortality rate associated with COPD, and a third of patients with this diagnosis die from cardiovascular complications [8, 16, 23].

Chronic diseases such as multifocal atherosclerosis (MAS) and COPD have a common pathogenetic mechanism, the basis of which is impaired oxygen supply, primarily to vital organs such as the heart and brain. Ischaemia caused by atherosclerotic damage to the arteries of many organs leads to the release of a number of substances into the peripheral blood, among which the neurotransmitters serotonin (S) and histamine (H) play a special role, the functional activity of which is aimed at improving the blood supply to ischemic organs. S and H are neurotransmitters in the cardiovascular system (CVS), myocardium, and gastrointestinal tract, as a result of which the generalisation of the atherosclerotic process with the involvement of many organs leads to an excessive pathological increase in the level of S and H in the peripheral blood. Excessively high levels of S and H lead to pathological reactions from the CVS and respiratory system, including changes in blood pressure, heart rate, and rhythm disturbances. In particular, it is known that an excessive increase in the concentration of these mediators can lead to pathological changes in haemodynamics, increased blood pressure, and the risk of recurrent myocardial infarction (MI), or ischaemic stroke (IS) [1—3, 7, 14]. Thus, the pathological process associated with atherosclerosis and fibrotic changes in the bronchopulmonary system recede into the background. Main pathogenetic link leading to cardiovascular events is the imbalance of neurotransmitters, primarily S and H. As evidenced by literature data, pathologically high levels of these neurotransmitters can lead to serotonin syndrome and histamine intoxication [4, 6, 9, 13, 19, 21].

Currently, there is a lot of literature data indicating possible changes in the cardiovascular and respiratory systems in various comorbid and functional conditions, while at the same time, functional activity can be directed in the opposite way [11, 17, 19, 21, 24].

In MAS, the instability of atherosclerotic plaques increases due to the activation of metallomatrix proteinases (MMP), increasing the risk of thrombosis and cardiovascular disasters [2, 7, 14].

The mechanism of action of H on the cardiovascular and respiratory systems is carried out by influencing metabolism and haemodynamics, through H1, H2, H3 and H4 histamine receptors. H has a special effect on the functional activity of the bronchopulmonary system and the microcirculatory system. Histamine acts as a key mediator that provides a connection between the respiratory system and cardiovascular pathology. In the respiratory tract, it increases bronchoconstriction, causes increased capillary permeability and increased oedema. In the vessels, it causes a two-phase effect: coronary vasoconstriction through H1 receptors and vasodilation through H2 receptors. In the process of atherosclerosis progression, these effects become destructive due to an increase in the risk of ischaemia and arrhythmias [9, 19, 22, 24].

Thus, MAS and COPD have a common pathogenetic basis, which is based on pathologically high activation of mediators, such as S and H. As a result of ischaemia of vital organs, protective mechanisms are activated aimed at ensuring regional blood flow to the ischaemic organ, which is manifested by the release of additional neurotransmitters, in particular, high levels of S and H. This interdependence requires an integrated approach to diagnosis and treatment, which will reduce systemic inflammation and improve the prognosis of patients with concomitant pathologies.

Objective — to optimise serotonin, histamine and metallomatrix proteinases levels in patients with multifocal atherosclerosis and chronic obstructive pulmonary disease.

Materials and methods

Our study included 68 male patients, mean age (67.5 ± 3.8) years with MAS and intermittent claudication syndrome (ICS). Patients were divided into 2 subgroups. MAS-1 group (n = 32): patients had clinical manifestations of ICS (stages I—II according to the Fontaine—Pokrovsky classification), 22 of them had a history of IS, 10 had a history of MI. Group MAS-2 (n = 36): all patients had ICS, COPD (GOLD 2, moderate severity (FEV1 from 50 to 79 % of the required, patient category B), 24 of them had a history of IS, 22 had a history of MI. Also, patients in groups MAS-1 and MAS-2 had concomitant pathologies: arterial hypertension in 14 and 17 patients, cigarette smoking (1 pack/day) in 18 and 31 patients, respectively. The control group (CG) consisted of 18 practically healthy individuals comparable in age (65.6 ± 4.2) and gender.

Exclusion criteria: ischaemic stroke within 1 year before inclusion in the study, haemorrhagic stroke in anamnesis, life-threatening cardiac arrhythmias (ventricular, prolongation of the Q-T interval), heart failure III stage and higher (according

Table 1. **Volumetric blood flow (FV, ml/min) in the studied vascular territories and their dynamics under the influence of treatment in the examined patients (Me (Q1; Q3))**

Vessels	CG (n = 18)	MAS-1 (n = 32)		MAS-2 (n = 36)	
		Before treatment	After treatment	Before treatment	After treatment
aCI	245.4 (183.5; 252.7)	180.2 (167.3; 221.4)***	215.8 (183.7; 247.1)#	177.3 (144.8; 218.6)***	197.5 (151.8; 209.4)#
aFC	202.6 (165.8; 219.4)	91.4 (78.3; 101.5)***	112.7 (68.4; 127.5)##	82.7 (67.4; 98.2)***	97.3 (81.8; 109.8)#
aTP	12.3 (8.8; 11.9)	3.9 (2.8; 5.4)***	5.7 (4.2; 8.6)##	3.5 (2.9; 4.4)***	5.1 (4.2; 7.9)##

Note. Significance of the differences in the indicator compared with the CG: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; Significance of the dynamics of indicators under the influence of treatment: # $p < 0.05$; ## $p < 0.01$; ### $p < 0.001$.

NYHA), bleeding in anamnesis, liver or kidney failure (creatinine clearance < 25 ml/min), uncontrolled hypertension, oncology.

All patients underwent a general clinical examination. The level of H and S was determined by ELISA in blood serum. Additionally, the level of S was determined in blood plasma (Sp) by ion-exchange chromatography. The levels of MMP-2 and MMP-9 were determined in blood plasma by ELISA. Considering that all patients had ICS, the ankle-brachial index (ABI) was determined. Using the method of ultrasound Doppler (HITACHI, ALOKA, AriettaS70), volumetric blood flow (FV) indicators were determined in the carotid arteries — *a. carotis interna* (aCI), lower limb arteries — *a. femoralis communis* (aFC) and *a. tibialis posterior* (aTP). Painless walking distance (PLWD) and maximum walking distance (MWD) were determined. Patients in the MAS-2 group, patients with COPD, were examined using the spirography method.

Regarding treatment, patients in both MAS groups received basic therapy, which included: acetylsalicylic acid (ASA), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs), calcium channel blockers, β-adrenoceptor blockers and, necessarily, statins [10, 15]. Additionally, patients received cilostazol (Cil) (50 mg twice a day), *GABA* — aminalon (A) (250 mg twice a day) and histidine decarboxylase inhibitor, catechin (C) — *Green T-Max* (1 capsule per day). Patients in the MAS-1 and MAS-2 groups were examined twice — before and 16 weeks after additional treatment. The CG was examined once, only at the initial examination.

Before inclusion in the study, all patients received information about the study and signed an informed consent to participate in the study. Our study complied with the ethical principles of the Declaration of Helsinki of the World Medical Association of Physicians (revision 2008), and with the ethical and moral requirements according to the Order of the Ministry of Health of Ukraine No. 281 dated 01.11.2000, including anonymity, confidentiality and benevolence.

Statistical analysis of data was performed using IBM SPSS, version 23, R. The normality of the distribution of the obtained data was determined by the Shapiro—Wilk test. For data with a normal distribution, the arithmetic mean value of the indicator (M) and standard deviation (± SD) were determined, and the Student's t-test was used to compare values. For non-normally distributed data, the Wilcoxon test was used to calculate the median, the first and third quartiles (Me (Q1; Q3) were calculated, and the paired-sample method was used to compare values; the χ^2 test and one-way analysis of variance were also used. The difference between data samples was considered significant at $p < 0.05$.

Results and discussion

According to the results of the initial examination of patients in both groups, significantly lower volumetric blood flow rates in all three examined vascular territories, compared to the CG, are noteworthy. As can be seen from Table 1, in the MAS-1 group, FV rates were lower than in the CG by 26.6 % in aCI, by 2.2 times in aFC, and by 3.1 times in aTP ($p < 0.001$ in all cases). In the MAS-2 group, peripheral haemodynamics rates showed worse indicators; FV in aCI was lower than in the CG by 27.8 % ($p < 0.001$), but especially in the arteries of the lower extremities: FV in aFC was 2.4 times lower, compared with the CG, and in aTP 3.5 times ($p < 0.001$ in both cases).

Worse haemodynamic indicators in patients of the MAS-2 group are comparable with the ABI, as an indicator of the generalisation of the atherosclerotic process. Thus, the ABI in the MAS-1 group was 0.78 ± 0.03, in the MAS-2 group 0.69 ± 0.02, and in the CG individuals it was 1.02 ± 0.05. Smoking, which was recorded in 86.1 % of patients of the MAS-2 group (31/36), as opposed to 56.3 % of patients of the MAS-1 group (18/31), which, according to the literature, increases the risk of atherosclerotic lesions of the arteries of the lower extremities [5, 8, 16, 20, 23].

According to Table 2, the histamine level in patients of both groups was significantly higher

Table 2. **Neurotransmitter levels in patients of both groups and their dynamics after treatment (Me (Q1; Q3))**

Measurements	CG (n = 18)	MAS- 1 (n = 32)		MAS 2 (n = 36)	
		Before treatment	After treatment	Before treatment	After treatment
Histamine, CU	0.53 (0.21; 0.72)	1.47 (0.87; 1.62)***	1.27 (0.76; 1.51)#	1.56 (0.91; 1.89)***	1.34 (0.82; 1.61)#
Serotonin (serum), CU	1.17 (0.67; 1.89)	2.02 (1.12; 2.24)**	1.81 (0.97; 2.01)#	2.09 (1.67; 2.31)**	1.87 (1.52; 2.07)#
Serotonin (plasma), μg/ml	5.31 (3.87; 7.21)	(n = 16) 13.11 (9.21; 19.42)***	(n = 16) 7.83 (5.71; 9.21)###	(n = 19) 15.32 (12.41; 18.19)***	(n = 19) 9.78 (8.41; 12.15)###
		(n = 16) 32.39 (15.81; 33.52)***	(n = 16) 14.51 (9.42; 16.19)###	(n = 17) 34.52 (16.48; 35.22)***	(n = 17) 14.22 (9.78; 17.16)###

Note. Significance of the differences in the indicator compared with the CG: * p < 0.05; ** p < 0.01; *** p < 0.001; Significance of the dynamics of indicators under the influence of treatment: # p < 0.05; ## p < 0.01; ### p < 0.001.

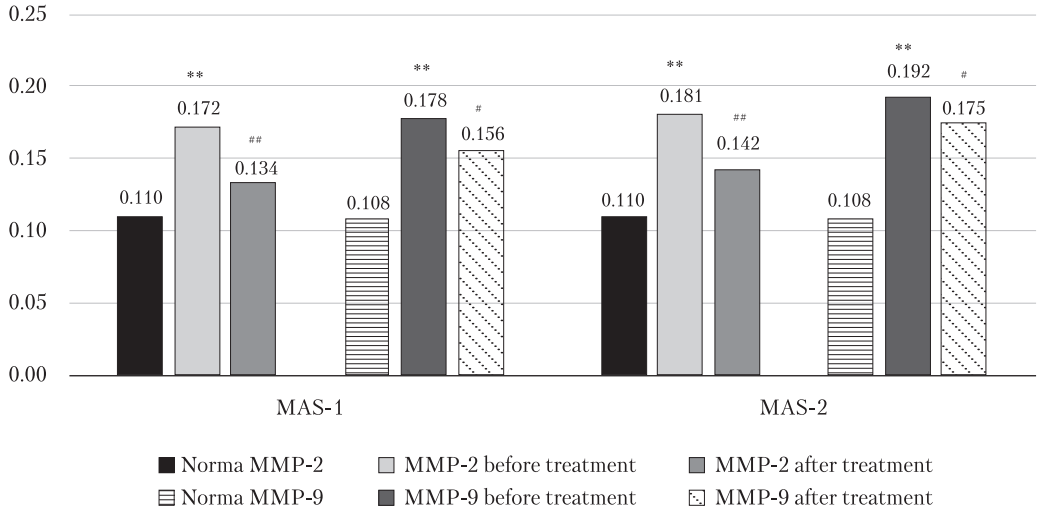

Fig. 1. **Levels of MMP-2 and MMP-9 (CU/ mg protein) in individuals of both groups, compared with the CG and their dynamics under the influence of treatment**

Note. Significance of the difference compared to the CG: * p < 0.05; ** p < 0.01; *** p < 0.001. Significance of the dynamics of indicators under the influence of treatment: # p < 0.05; ## p < 0.01; ### p < 0.001.

compared to the CG. In patients of the MAS-1 group, the histamine level was 2.8 times higher ($p < 0.001$) compared to the CG, and in the MAS-2 group, it was 2.9 times ($p < 0.001$) compared to the CG. Our data are comparable with the literature data on excessively high histamine levels in patients with MAS, taking into account the influence of mast cells on the development of the atherosclerotic process [12, 17].

The level of the neurotransmitter S, both in plasma and in serum, significantly exceeded the CG indicators. The level of S in the serum, Ss, in the MAS-1 group was 72.6 % higher, and in the MAS-2 group was 78.6 % higher, compared to the CG ($p < 0.001$ in both cases). In blood plasma, Sp, levels were recorded 2.5 times higher in the MAS-1 group and 2.9 times higher in the MAS-2 group, compared to the CG data, as well as morning S peaks, in particular, in the MAS-1 group (n = 16) by 6.0 times and in the MAS-2 group (n = 17) by 6.5 times higher, compared to the CG ($p < 0.001$ in all cases).

According to the data of Fig. 1, we see significantly high levels of MMP-2 and MMP-9, compared with the CG. In patients of the MAS-1 group, the levels of MMP-2 were 56.4 %, MMP-9 — 64.8 % higher, compared with the CG, and in patients of the MAS-2 group: 64.5 and 77.8 %, ($p < 0.01$ in all cases) respectively.

After the treatment with the addition of Cil, A, and C, we observed an improvement in the clinical picture of the patients and an approach to the reference values of the levels of neurotransmitters and MMP. As for the clinical picture of the patients, in both groups of MAS, ICS began to bother less, paresthesias, numbness, tingling sensations in the lower extremities began to be noted less often by the patients. We confirmed the obtained results by increasing the walking distance: in the MAS-1

group, PLWD increased by 68.2 %, and in the MAS-2 group by 67.4 %, MWD: by 43.1 and 41.2 %, ($p < 0.01$ in all cases), respectively. Clinical symptoms also improved in patients with COPD, in patients of the MAS-2 group, the frequency of morning cough attacks decreased, shortness of breath decreased. As can be seen from Fig. 2, an increase in FEV1 by (11.8 ± 0.2) %, compared with the initial data, an increase in air flow and volume.

Volumetric blood flow indicators improved in all studied vascular territories. In patients of the MAS-1 group, FV increased in aCI by 19.7 % ($p < 0.05$), in aFC by 23.3 % ($p < 0.01$), in aTP by 46.1 % ($p < 0.01$), in the MAS-2 group by 11.4 % ($p < 0.05$), 17.7 % ($p < 0.05$), 45.7 % ($p < 0.01$), respectively.

We observed a decrease in H levels by 13.6 % in the MAS-1 group and by 14.1 % in the MAS-2 group ($p < 0.05$ in all cases). S levels, in particular the morning peak S levels determined in blood plasma, after treatment significantly decreased in the MAS-1 group by 40.3 % (n = 16) and by 2.2 times (n = 16), in the MAS-2 group by 36.2 % (n = 19) and by 2.4 times (n = 17), ($p < 0.001$ in all cases). Average daily S levels determined in blood serum decreased by 10.4% ($p < 0.05$) in the MAS-1 group and by 10.5% ($p < 0.05$) in the MAS-2 group, compared with the data before taking additional treatment.

As can be seen from Fig. 1, the levels of MMP-2 and MMP-9 after treatment significantly decreased in both groups of patients. In MAS-1 group patients, the level of MMP-2 decreased by 22.1 % ($p < 0.01$) and MMP-9 by 12.4 % ($p < 0.05$), compared to initial data; in patients in the MAS-2 group: by 21.5 % ($p < 0.01$), and 8.9 % ($p < 0.05$), respectively.

Our study demonstrates the importance of diagnosis and combined treatment of patients with combined pathology of MAS and COPD. Patients with COPD have an increased risk of developing MAS due to chronic inflammation, hypoxia and activation of mast cells. In turn, atherosclerosis complicates the course of COPD, contributing to impaired oxygen delivery to tissues.

Our studies have shown that patients with MAS with an injury of the cerebral, coronary, femoral arterial territories in combination with COPD represent a special clinical form. Simultaneous damage of the CVS and respiratory organs leads to a breakdown of compensatory and protective mechanisms aimed at eliminating hypoxia and ischaemia. The data we obtained show reduced FV indicators in all studied territories and excessively high levels of S, H, MMP-2 and MMP-9, compared with CG.

First of all, this is manifested by an increase in the levels of S and H in the peripheral blood,

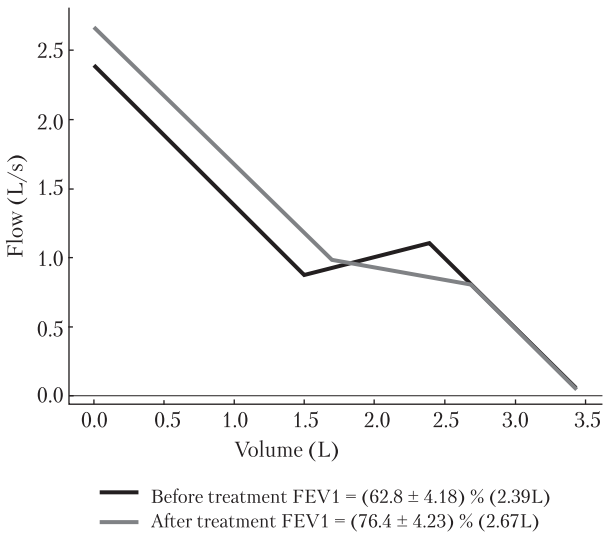

Fig. 2. **Spirometry curve in patients in the MAS-2 group before and after treatment**

S increases 5—7 times, compared with reference values in the morning hours with a stable two-times increase during the day — a condition that is considered as serotonin syndrome. Serotonin plays a key role in the regulation of vascular tone, platelet aggregation and blood circulation. In patients with MAS, an increase in serotonin levels is observed, which contributes to vasoconstriction, thrombus formation and progression of ischemic lesions [2, 3, 14]. In COPD, serotonin can affect the strengthening of inflammatory processes and contribute to the development of pulmonary hypertension through stimulation of vascular smooth muscle cells [6, 13].

Morning peak S increases were comparable with pathologically high levels of H, which in some cases reached levels of histamine intoxication. In patients with MAS, the level of H was significantly higher, which correlates with the formation of atherosclerotic plaques, ischaemic processes in the myocardium and impaired vascular permeability [11, 24]. COPD is also accompanied by increased levels of histamine, which is associated with inflammatory activity in the bronchi, vasodilation and the involvement of immune cells. In patients with COPD, histamine activates bronchial smooth muscle cells through H1 receptors, causing bronchospasm, and also contributes to chronic inflammation in the airways [4, 19, 24].

Our studies have shown that increased levels of S and H were combined with high increases in MMP-2 and MMP-9, for which S and H were direct and key activators of MMP, which in turn increases the risk of destabilisation of atherosclerotic plaques [1, 18]. In this case, we are inclined to consider the described condition of patients with MAS and COPD as a high risk of cardiovascular events.

Therefore, it was important for us to influence the pathophysiological links of MAS, taking into account comorbid pathology, in this case COPD. Secondary prevention of cardiovascular events in patients with MAS, presented in the Guidelines [10, 15], including dual antiplatelet therapy, statins, antihypertensive drugs. Basic therapy is necessary, but not sufficiently effective in patients with combined pathology of MAS and COPD, which is manifested by the lack of effect on high levels of S and H in peripheral blood.

We were the first to use a combination of Cil, Am additionally to basic therapy. Our studies have shown that the use of Cil allows to eliminate morning stiffness and avoid the development of serotonin syndrome, in our opinion, one of the main factors in the development of repeated cardiovascular events. In addition, the use of Cil is recommended (class 1A) to increase walking distance in patients with peripheral atherosclerosis [10]. The use of a combination of Cil and GABA, according to our data, reduces and stabilises S levels in both groups of patients.

But this combination does not affect high levels of H, in connection with which, we used histidine decarboxylase blockers — Catechin. It is known that different levels of S and H can differently affect changes in metabolism, haemodynamics, organ function, in connection with which, we focused our attention on ways to reduce pathologically high levels of H by using 1 of the histidine decarboxylase blockers, the main enzyme in the conversion of histidine to histamine. It is important that H is formed from the essential amino acid histidine, and the process of converting histidine to histamine occurs due to the intestinal microbiota and products rich in histidine. In connection with which, in our study, we used a dual method — a diet without a high content of histidine and a drug - catechin. As a result of the treatment, the level of H decreased ($p < 0.05$ in all cases) by 13.6 % in the MAS-1 group and by 14.1 % in the MAS-2 group. These changes led to a decrease in COPD symptoms in patients in the MAS-2 group, in the form of a decrease in the frequency of morning cough attacks, a decrease in shortness of breath and an increase in FEV1 according to spirometry by 11.8 %, compared with baseline data.

Our study has shown that the use of Cil allows you to eliminate morning increases and avoid the development of serotonin syndrome, one of the main factors in the development of repeated cardiovascular events (ischemic stroke, MI), as well as improve blood supply in all affected vascular territories and reduce the levels of MMP-2 and MMP-9 in peripheral blood. The use of a combination of Cil and GABA, according to our data, reduces and stabilises S levels in both groups of patients. The addition of catechins, one of the most active blockers of histidine decarboxylase, to Cil and GABA led to a decrease in the level of H in peripheral blood. Clinically, this was manifested by improved respiratory function and increased pain-free walking distance.

Conclusions

We believe that determining and correcting the state of neurotransmitter supply in patients with MAS and COPD is an important component of increasing the effectiveness of therapy and improving secondary prevention of serious cardiovascular events.

Conflict of interest. The authors of this manuscript claim that there is no conflict of interest during the research and writing of the manuscript.
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Нова концепція вторинної профілактики серцево-судинних подій у хворих на мультифокальний атеросклероз, ускладнений хронічним обструктивним захворюванням легень

Вторинна профілактика серцево-судинних подій, особливо в пацієнтів із поєднаною патологією мультифокального атеросклерозу (МАС) та хронічного обструктивного захворювання легень (ХОЗЛ) є актуальною медичною проблемою. Ішемія життєво важливих органів спричиняє патологічно високий викид нейромедіаторів, тому пошук нових стратегічних підходів, які будуть здатні стабілізувати цей стан, є надзвичайно актуальною.

Мета роботи — оптимізувати рівні серотоніну, гістаміну та металоматриксних протеаз (ММП) у пацієнтів із МАС та ХОЗЛ.

Матеріали та методи. У дослідження було залучено 68 пацієнтів чоловічої статі (середній вік — (67,5 ± 3,8) року) з ураженням церебрального, коронарного та феморального судинних басейнів і виявами синдрому переміжної кульгавості. Пацієнтів розподілили на дві групи. У групі МАС-1 (n = 32) пацієнти мали лише МАС, у групі МАС-2 (n = 36) — також ХОЗЛ (GOLD 2). Контрольна група утворена із 18 практично здорових чоловіків (середній вік — (65,6 ± 4,2) року). Визначали кісточково-плечовий індекс, рівень серотоніну, гістаміну, ММП-2 і ММП-9 у крові, дистанцію безбольової ходьби, проводили доплерографію судин шиї та артерій нижніх кінцівок, спірографію. Пацієнтам обох груп на тлі базового лікування призначали цилостазол (50 мг двічі на добу), γ-аміномасляну кислоту — «Аміналон» (250 мг двічі на добу), катехін — «Green T-Max» (1 капсула на день). Курс лікування — 16 тиж.

Результати та обговорення. Первинне обстеження пацієнтів обох груп виявило статистично значущо ($p < 0,01$) вищі рівні нейромедіаторів серотоніну, гістаміну, ММП-2 і ММП-9 порівняно з контрольною групою, ранкові піки вмісту серотоніну в плазмі крові більші в 5—7 разів. Показники об'ємного кровотоку були статистично значущо ($p < 0,01$) нижчими порівняно з контрольною групою. Завдяки лікуванню вдалось усунути ранковий 5—7-разовий підйом рівня серотоніну, уникнути розвитку серотонінового синдрому, поліпшити кровопостачання в усіх уражених судинних басейнах. Статистично значущо ($p < 0,05$) збільшився об'ємний кровотік і зменшився рівень ММП-2 ($p < 0,001$) та ММП-9 ($p < 0,01$) у периферичній крові. Комбінація цилостазолу, γ-аміномасляної кислоти й катехіну статистично значущо ($p < 0,05$) знижувала та стабілізувала концентрацію серотоніну та гістаміну в крові в обох групах пацієнтів. Про це свідчило поліпшення функції зовнішнього дихання та збільшення дистанції безбольової ходьби.

Висновки. В основу роботи було покладено новий напрям вторинної профілактики серйозних серцево-судинних подій, що ґрунтується на корекції порушень нейромедіаторної регуляції (серотонін і гістамін). Надвисокий рівень серотоніну та гістаміну був скоригований застосуванням комбінації цилостазолу, γ-аміномасляної кислоти й катехіну, що дало змогу стабілізувати та поліпшити клінічний стан хворих на МАС і ХОЗЛ.

Ключові слова: хронічне обструктивне захворювання легень, мультифокальний атеросклероз, серотонін, гістамін, металопротеази.

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