Current Issues of Familial Hypercholesterolemia: Features of Disorders of The Sympathetic Adrenal System and Cytokine Status

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ABSTRACT

Presented the violations of the sympathetic adrenal system and cytokine status in patients with coronary heart disease in the family hypercholesterolemia. 154 men and women at the age of 18 to 65 years, with an average age 43,8 ±7,2 years and 15 practically healthy persons aged 20 to 50 years, with an average age 41,4 ±3,5 of the. Clinical, instrumental and special research methods were carried out. It was revealed that in the art of hypercholesterinemia, the pronounced changes of sympathetic adrenal system and cytokine status, which are more pronounced extent in patients with family hypercholesterolemia with clinical signs of CHD.

Keywords: Family hypercholesterolemia, coronary heart disease, sympathetic adrenal system, catecholamines, cytokines.

In recent years, there has been a re-evaluation of the key provisions of the pathogenesis of atherosclerosis and coronary heart disease. It has been established that inflammation is the most important sign of the development of atherosclerosis, which can determine its progression and lead to vascular dysfunction and plaque rupture, followed by thrombotic occlusion and the development of cardiovascular complications (Alekperov E. Z. et al., 2014; Centurion O..A., 2016). It has been established that the effect of hyperproduction of proinflammatory cytokines on the progression of CHD is realized by direct damaging effects exerted primarily by tumor necrosis factor-a(TNF-a), interleukins (IL) -1, -6 on cardiomyocytes and peripheral tissues of the human body, modulation of the activity of neurohumoral systems (in particular, CAC and RAAS), production of nitric oxide (NO) and other metabolic factors. Recent studies suggest that understanding the pathogenesis of CHD requires further study of circulatory regulatory systems, in particular the sympathetic-adrenal system (CAS). Data on the effect of catecholamines (CA) on the development of cellular or humoral immune responses are scarce. According to them, it can be assumed that as a result of the development of the stress response, the processes of immuno-inflammatory reactions are suppressed.

Objective: To study the state of SAS and levels of pro-and anti-inflammatory cytokines in CHD patients with familial hypercholesterolemia (FH).

Materials And Methods

The study included 154 people with AHS: 102 men, 52 women aged 18 to 65 years, with an average age of 43.8±7.2 years, and 15 practically healthy individuals aged 20 to 50 years, with an average age of 41.4±3.5 years. The study included patients over 18 years of age with definite and probable CHD, according to the criteria of the Dutch Lipid Clinic Network (DLCN), depending on the manifestations of clinical signs of CHD, the subjects were randomized into 3 groups: I-control, healthy, n=15; II-CHD without signs of CHD, n=56 (38.9%III-AHS with signs of CHD, n=98 (61.1%). Total cholesterol, high – density lipoproteins (HDL), and triglycerides (TG) were determined

using biochemical rapid analyzers "Reflotron Plus" ("Rowithhe", Germany). The content of LDL and VLDL was calculated according to the formula of A. N. Klimov. Daily urinary excretion of free and conjugated forms of catecholamines (CA) was studied by fluorimetric method.

Determination of LPO products in blood serum was performed by the method of B. V. Gavrilov. Determination of MAO in blood serum was carried out by the method of A. I. Balakleevsky. Cytokine status was determined by the level of interleukins IL-6, IL-10, and TNF-α in blood serum by solid-phase enzyme immunoassay. Non-specific inflammation was determined by the level of highly sensitive C-reactive protein (hf-CRP) by the immunoturbodimetric method using Vector-Best kits (Novosibirsk, Russia). CStatistical processing of the obtained results was carried out using Student's criteria.

Results And Discussions

Comparative characteristics of the blood lipid spectrum indicators of the studied groups are shown in Table 1.

Table 1

Some clinical and biochemical parameters of lipids and lipid peroxidation products in the blood serum of patients with CHD and healthy subjects (P<0.001).

Indicators	Healthy indicators (n=15)	AHS without CHD (n=56)	AHS with CHD (n=98)
Tendon xanthomas, abs (%)	-	44 (78,6)	89 (91)
TC, mmol/L	4,5±0,3	7,5±1,2*	8,23±1,3^
TG, mmol/L	1,3±0,1	1,6±0,1*	1,8±0,1^
LDL CHOLESTEROL, mmol/L	3,1±0,3	6,3±0,4*	6,9±0,4^
HDL CHOLESTEROL, mmol/L	1,3±0,1	1,0±0,1*	1,1±0,1^
VLDL CHOLESTEROL, mmol/L	0,28±0,02	0,34±0,02*	0,36±0,02^
IA, u	3.1±0,1	6.4±0,2*	6.7±0.2^
MDA, nmol/L	3,6±0,5	6,2±0,8*	7.8±0.7^

Note: IA - atherogenicity index; MDA – malondialdehyde;*, ^ - differences in relation to the control group are significant (P<0.001).

When studying the daily excretion of CA and DOPA, the following changes were observed (Table 2). In IIGroup II, there was a statistically significant (p<0.001) increase in the daily excretion of epinephrine (A) free by 24.4%, conjugated by 28.9% and total by 26.5% in relation to the control group. The excretion of free norepinephrine (HA) increased by 12.1%, conjugated - by 16.8% and total-by 14.4% in relation to the control group (p<0.001). Dopamine (DA) free, conjugated, total increased by 8.5%, 10,%, and 9.3%, respectively, in relation to the control group (p<0.05). DOPA increased by 4.5% in relation to the control group (p<0.001). In IIIgroup III, there was a decrease in the daily excretion of catecholamines, in particular; free by 31.1%, conjugated by 23.7%, total by 27.7% in relation to the control group (p<0.001). Free, conjugated, and total weight was reduced by 31.3%, 25.3%, and 29.3%, respectively, compared with healthy subjects (p<0.001). There is a decrease in DA excretion: free - by 51.1%, conjugated - by 46.6%, total-by 48.8% in relation to the control (p<0.001). DOPA was reduced by 22.0% compared to group I (p<0.001).

The study of MAO activity in patients with AHS revealed a significant decrease in the activity of the enzyme in all the examined groups in relation to the control group (Table 2). In the control group, MAO activity was 0.07 ± 0.001 u / ex. In IIgroup II, MAO activity was 0.05 ± 0.003 u / ex, which is 28.6% lower than the control (p<0.001). In IIIgroup III, there was a significant decrease in the activity of the

enzyme by 42.9% compared to the control group and amounted to 0.04 ± 0.004 u / ex. ($p<0.001$).

Indicators of LPO in all study groups significantly differed from those in the control group. In the control group, the level of malondialdehyde(MDA), a secondary product of LPO, ranged from 2.1 – 4.4 nmol/ml, with an average of 3.6±0.5 nmol/ml. In group II, there was a statistically significant increase in the level of MDA by 72.2% compared to the control group ($p<0.001$). In IIIGroup III, there was an increase in the level of MDA by 116.6 % in relation to the control indicators ($p<0.001$) (Table 1).

Table 2

Daily excretion of CA and MAO activity in healthy subjects and patients with CHD, P<0.001

Group	A, mcg / day	NA, mcg / day	DA, mcg / day	DOPA, mcg / day	MAO, u / ex
I-Control				46.4±0.6	0.07±0.001
free	4.5±0.1	9.9±0.1	140.4±5.2		
conjugated	3.8±0.1	8.7±0.1	152.8±5.5		
total	8.3±0.2	18.8±0.2	292.2±9.4		
II-**CHD without CHD**				48.5±0.8	0.05±0.003
free	5.6±0.1	11.1±0.1	152.4±6.3		
conjugated	4.9±0.1	10.4±0.1	167.0±5.2		
total	10.5±0.2	21.5±0.4	319.4±10.0		
III-**CHD with CHD**				36.2±0.6	0.038±0.003
free	3.1±0.1	6.8±0.1	68.6±3.2		
conjugated	2.9±0.1	6.5±0.1	81.1±4.1		
total	6.0±0.2	13.3±0.2	149.7±7.4		

Special attention was paid to the study of vanillylmindalic acid (VMC), the end product of the metabolism of the catecholamines epinephrine and norepinephrine. The level of IUD was determined by the level of urinary excretion. In the body, IUD is formed from epinephrine and norepinephrine indirectly through intermediate metabolites such as dihydrooxyphenyl glycol (DHPG), methanephrine, and normetanephrine.

Table 3

Daily excretion of vanillylmindalic acid in patients with CHD without and with CHD, (mg/day), P<0.001

Indicators	of the Group of patients			
	with CHD without CHD (n=56)	AHS with CHD (n=98)	Control (n=15)	P

Vanillylmindalic acid, IUD (mg / day)	12,4±2,1	15,2±2,3	7,1±0,9	<0,001

Comparative evaluation of indicators of daily excretion of urine vanillylmandelic acid (VMK) healthy and FHC patients without clinical signs of coronary artery disease and clinical signs of coronary heart disease have shown that in patients with FHC without CHD levels daily excretion was 12.4±2.1, the FHC patients with CHD of 15.2±2.3 years respectively 1.75 times (74.6%) (p<0,001) and 2.14 times (114,0%) (p<0,001) more than the control (tab. 3). As expected trend in a more pronounced degree observed in known that cytokines indirectly involved in the regulation of most of FHC patients with clinical signs of ischemic heart disease (table. 3).

According to the literature data on biochemical processes in the body: cholesterol metabolism, formation and inactivation of free radicals, vascular wall remodeling reactions, but there is insufficient data on the direct relationship of the role of cytokine regulation in atherogenesis. In this regard, the study of cytokine status a in familial hypercholesterolemia was of particular interest.

In our study, indicators of non – specific inflammation-cytokines: IL-6, IL-10, TNF-α, and hf-CRP-were evaluated in patients with AHS.

Table 4

Indicators of cytokines IL-6 and IL-10 in blood serum in patients with CHD without CHD

Indicators	of the Group of patients		
	with CHD without CHD (n=56)	Control (n=15)	P
IL-6 (pg/ml)	15.3±2.1,1	8.5±0.9	<0.001
IL-10 (pg/ml)	8.4,4±0.4	8.22±0.7	>0.05

Table 5

Indicators of cytokines IL-6 and IL-10 in blood serum in patients with CHD

Indicators	of the Group		
	of CHD patientswith CHD (n=98)	Control (n=15)	R
IL-6 (pg / ml)	24,5±0,9	8,5±0,9	<0,001
IL-10 (pg / ml)	8.1±0.7	8.22±0.7	>0.05

During the study, a significant increase in the proinflammatory cytokine IL-6 was recorded. An increase in IL-6 values indicates the maintenance of chronic inflammation in the arterial wall in familial hypercholesterolemia. In turn, there is a slight decrease in the content of anti-inflammatory cytokines IL-10, which may indicate an indirect violation of the anti-inflammatory mechanisms of immunoreactivity and inhibition of the function of T-regulatory cells in familial hypercholesterolemia (Table 4,55).

БTNF-α and hf-CRP were studied in patients with AHS without and with CHD. A

comparative assessment of TNF-α and hf-CRP values in blood serum in healthy and AHS patients without clinical signs of CHD showed that in patients with AHS, the levels of TNF-α and CRP were 13.4±2.2 and 2.7±0.1, which is 1.76 times (p<0.001) and 2.5 times (p<0.001 6). Such trends are more pronounced in the group of patients with CHD with clinical signs of CHD (Table 6). Thus, the level of TNF-α in patients averaged 18.5±1.8, which is 2.4 times higher (p<0.001) than in the control group, and the level of TNF-α in patients with CHD is more pronounced. The average value of hf-CRP was 3.8±0.1 mg / ml, which is 3.45 times higher (p<0.001) than the control parameters.

Table 6

TNF-α and hf-CRP values in blood serum in patients with AHS

Indicators	of the Group of examined patients			
	with CHD without CHD (n=56)	AHS with CHD (n=98)	Control (n=15)	P
TNF-α (pg / ml)	13,4±2,2	18,5±1,8	7,6±0,7	<0,001
hf-CRP (mg / ml)	2,7±0,1	3,8±0,1	1,1±0,1	<0,001

Thus, the problem of the functional state of SAS in patients with CHD, its relationship with the features of the course of the disease, the formation of complications is the subject of discussion. One of the central places in the complex interaction of various regulatory systems belongs to SAS, which is associated with the widest range of its effects [6]. Activation of SAS, through direct trophic effects, is accompanied by a number of structural changes, primarily in the vascular wall and myocardium. Structural changes in blood vessels are directly involved in the formation of myocardial ischemia, stroke, and damage to other target organs [11].

An increase in the activity of SAS in familial hypercholesterolemia can be regarded as compensatory, ensuring the mobilization of the body's defenses, increasing the energy supply to the myocardium. A further increase in the intensity of CAC activity is aimed at mobilizing the internal reserves of the body. However, at one of the stages of this process, the catabolic orientation of the effects of SAS begins to manifest, and the further increase in the activity of which becomes one of the main elements of the formation of CHD and its complications.

The results of the conducted studies showed that in case of AHS, there is a moderate activation of CAC associated with an increase in the excretion of catecholamines: A, HA, DOPA by 1.27; 1.14; 1.05 times, respectively (p<0.001), DA by 1.09 times (p<0.05) in relation to healthy people. These data coincide with the data of L. M. Doborjiginidze, N. A. Graziansky et al., and A. I. Nesterova (2000). In turn, in patients with CHD in patients with chronic forms of CHD, there is an equivalent decrease in the daily excretion of catecholamines: A, NA, DA by 1.38; 1.41; 1.96 times, respectively (p<0.001), DOPA by 1.28 times (p<0.05) in relation to the control. In patients with CHD with chronic forms of CHD, inhibition of CAC activity is manifested by a decrease in the hormonal and neurotransmitter link, as well as a decrease in reserve capabilities due to a decrease in the release of DOPA (p<0.05) and dopamine (p<0.001). It is known that a decrease in the level of catecholamines in cardiovascular diseases can be a predictor of the development of arrhythmias, asystoles, and the threat of sudden death in stressful situations [10].

Currently, it is reliably known that the activation of free-radical peroxide processes underlies the pathogenesis of many diseases of internal organs. LPO processes cause the

accumulation of oxidized LDL, which leads to microcirculation disorders [10]. From this point of view, the study of LPO processes in patients with AHS has become particularly interesting, since the main biochemical indicator of blood is an increase in LDL. It was found that in CHD and atherosclerosis, LPO increases. The intensity of LPO reflects the degree of metabolic disorders in the body [8]. Our results indicate an increase in LPO processes in CHD without CHD by 1.72 times ($p<0.001$), and the most pronounced intensification of LPO processes is observed in chronic forms of CHD, exceeding the control indicators by 2.16 times ($p<0.001$).

As is known, under the conditions of lipid peroxidation, the key enzyme of biogenic amine oxidation, MAO, can undergo a significant transformation of its catalytic properties, as a result of which its activity to monoamines decreases [7]. We studied the activity of MAO in healthy and AHS patients with CHD and without clinical manifestations of CHD. During observation, it was found that the functional activity of MAO in healthy and AHS patients with CHD and without clinical manifestations of CHD. MAO undergoes significant changes depending on the degree of manifestation of cardiovascular pathology. Thus, in patients with AHS without clinical forms of CHD, there is a decrease in MAO activity by 1.4 times ($p<0.001$). The lowest activity of the enzyme, which is 1.75 times ($p<0.001$) lower than that of the control group, is observed in patients with AHS with CHIBS, which confirms a qualitative violation of its catalytic properties.

The results obtained indicate that y in patients with familial hypercholesterolemia, a statistically significant, strong positive association of A and NA with the level of cytokine IL-6 ($r=0.97$ and $r=0.94$; $p<0.01$) and cytokine IL-10 ($r=0.93$ and $r=0.94$; $p<0.01$) is clearly traced. Therefore, cytokines are certainly the leading factors of impaired SAS activity, including in the case of AHS.

Thus, the data obtained revealed that the development and progression of CHD in AHS is accompanied by impaired functioning of the SAS. Increased sympathetic tone leads to a whole range of metabolic, trophic and hemodynamic changes, which is accompanied by an increased risk of cardiovascular accidents in patients with CHD. The results of our studies, to some extent, can show the important role of impaired SAS activity and LPO processes in the development of CHD and its complications in CHD.

In general, it can be assumed that among the important factors, the difference in the deterioration of the dynamics of neurohumoral indicators of interleukin status, lipid parameters, and the development of ischemic disease in AHS was associated with indicators that characterize non-specific inflammation and, above all, TNF-α and hf-CRP. The study clarified the functional imbalance between pro- and anti-inflammatory mechanisms of the immune response in SGH, revealed mutually regulating relationships between cytokines, total blood cholesterol levels, and indicators of the functional state of the sympathoadrenal system, in particular, the level of catecholamine excretion, IUD, and MAO levels in the blood.

Determination of lipid metabolism parameters, study of the state of CAC, MAO activity, LPO processes, and features of changes in cytokine status can provide additional information for early diagnosis of CHD and atherosclerosis in relatives with CHD, and assessment of the severity of CHD and atherosclerosis in CHD.

Conclusions

1. A comprehensive study of individuals with AHS without clinical manifestations of CHD showed an increase in the excretion of epinephrine, norepinephrine, dopamine, and DOPA by 26,5%, 14,4%, 9,3%, 4,5% accordingly, in relation to healthy people, which indicates the activation of the hormonal link of CAC, and therefore its early correction is necessary to prevent the development of coronary heart disease.
2. A comprehensive study of AHS patients with chronic forms of CHD revealed a decrease in the excretion of epinephrine, norepinephrine, dopamine, and DOPA by 27,7%, 29,3%, 48,8%, 22,0% accordingly, in relation to the control group, it indicates a decrease in the activity of the hormonal,

mediator link and reserve capabilities of the CAC.

3. In the studied patients with AHCS, there is a significant decrease in MAO activity in relation to healthy ones, which indicates a qualitative change in the catalytic properties of the enzyme.
4. A comparative assessment of the daily urinary excretion of vanillylmindal acid (BMC) in healthy and AHS patients without clinical signs of CHD and clinical signs of CHD showed that in patients with AHS without CHD, the daily excretion levels were 12.4±2.1, in patients with AHS with CHD 15.2±2.3,which is 1.75 times (by 74.6%), respectively ($p<0.001$) and 2.14 times (by 114.0%) ($p<0.001$) more than the control indicators.
5. In patients with familial hypercholesterolemia, a highly reliable, strong positive association of A and NA with the level of cytokine IL-6 ($r=0.97$ and $r=0.94$; $p<0.01$) and cytokine IL-10 ($r=0.93$ and $r=0.94$; $p<0.01$) is clearly traced.
6. A comparative assessment of TNF-α and hf-CRP values in blood serum in healthy and AHS patients without clinical signs of CHD showed that in patients with AHS, the levels of TNF-α and CRP were 13.4±2.2 and 2.7±0.1, which is 1.76 times ($p<0.001$) and 2.5 times ($p<0.001$) more control indicators, more pronounced changes are observed in the group of patients with CHD with clinical signs of CHD.

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