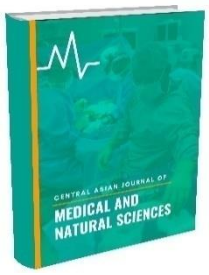
CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES



Volume: 02 Issue: 05 | Sep-Oct 2021 ISSN: 2660-4159

http://cajmns.centralasianstudies.org

Features Violations of the Sympathetic Adrenal System and Cytokine Status in Patients with Coronary Heart Disease in the Family Hypercholesterolemia

1. **Bakhrom Mo'minjanovich Vakhobov**
2. **Mamazoir Ahmedovich Ho'jamberdiev**

Received 27th Aug 2021,
Accepted 29th Sep 2021,
Online 26th Oct 2021

[1] Assistant Professor, Andijan State Medical Institute, Uzbekistan

[2] Professor, Andijan State Medical Institute, Uzbekistan

Abstract: Presented the violations of the sympathetic adrenal system and cytokine status in patients with coronary heart disease in the family hypercholesterolemia. 144 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.

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

Introduction: In recent years, there has been a reassessment 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 with subsequent thrombotic occlusion and the development of cardiovascular complications (Alekperov E.Z. et al., 2014; Centurion OA, 2016) ... It was found that the effect of overproduction of proinflammatory cytokines on the progression of IHD is realized through a direct damaging effect exerted primarily by tumor necrosis factor-a (TNF-a), interleukins (IL) -1, -6 on cardiomyocytes and peripheral tissues of the human body, modulating the activity of neurohumoral systems (in particular SAS and RAAS), production of nitric oxide (NO) and other metabolic factors. Recent studies indicate that in order to understand the pathogenesis of ischemic heart disease, further study of circulatory regulation systems, in particular the sympathetic-adrenal system (SAS), is necessary. There are few data on the effect of catecholamines (CA) on the development of a cellular or humoral immune response. According to them, it can be assumed that as a result of the development of a response to stress, the processes of immune-inflammatory reactions are suppressed.

Purpose of the study: To study the state of SAS and the levels of pro- and anti-inflammatory cytokines in patients with coronary artery disease with familial hypercholesterolemia (FHC).

Material and methods: 144 people with FHC were examined: 96 men, 48 women aged 18 to 65 years, whose average age was 43.8 ± 7.2 years, and 15 practically healthy individuals aged 20 to 50 years old, with an average age of 41.4 ± 3.5 years. The study included patients over 18 years old with definite and probable FHC, according to the criteria of the Dutch Lipid Clinic Network (DLCN). Depending on the manifestation of clinical signs of coronary artery disease, the subjects were randomized into 3 groups: I - control, healthy, n = 15; II - CGHS without signs of ischemic heart disease, n = 56 (38.9%); III - CHS with signs of ischemic heart disease, n = 98 (61.1%). Determination of total cholesterol, high density lipoproteins (HDL), triglycerides (TG) was carried out with biochemical express - analyzers "Reflotron Plus" ("Roche", Germany). The content of LDL, VLDL was calculated using the formula of A.N. Klimov. The daily urinary excretion of free and conjugated forms of catecholamines (CA) was studied using the fluorometric method.

The determination of lipid peroxidation products in blood serum was carried out according to the method of B.V. Gavrilov. Determination of MAO in blood serum was carried out according to the method of A.I. Balakleevsky. The cytokine status was determined by the level of interleukins IL-6, IL-10, TNF-α in the blood serum by the method of enzyme-linked immunosorbent assay. Nonspecific inflammation was determined by the level of highly sensitive C-reactive protein (hs-CRP) by immunoturbodimetric method using the kits of the "Vector-Best" company (Novosibirsk, Russia). Statistical processing of the obtained results was carried out using Student's criteria.

Result and discussion:

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

Table 1: Some clinical and biochemical parameters of lipids and LPO products in the blood serum of those examined with FHC and in healthy subjects (P <0.001).

Indicators	Healthy (n=15)	SGHS without ischemic heart disease (n = 56)	SGHS with ischemic heart disease (n=98)
Tendon xanthomas, abs (%)	-	44 (78,6)	89 (91)
Total cholesterol, 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, units	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 - atherogenic index; MDA - malondialdehyde; *, ^ - differences in relation to the control group are significant (P <0.001).

When studying the daily excretion of CA, DOPA, the following changes are observed (Table 2). In group II, there was a statistically significant (p <0.001) increase in the daily excretion of free adrenaline (A) by 24.4%, conjugated by 28.9% and total by 26.5% in relation to the control group. The excretion of free norepinephrine (NA) 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%; ten,%; 9.3%, respectively, in relation to the control (p <0.05). DOPA increased by 4.5% in relation to the control group (p <0.001). In group III, there is a decrease in the daily excretion of catecholamines, in particular; And free by 31.1%, conjugated by 23.7%, total by 27.7% in relation to the control group (p <0.001). HA free, conjugated, total decreased by 31.3%, 25.3%, 29.3%,

respectively, compared with healthy subjects (p <0.001). There is a decrease in the excretion of DA: free - by 51.1%, conjugated - 46.6%, total - by 48.8% in relation to the control (p <0.001). DOPA decreased by 22.0% in relation to group I (p <0.001).

In the study of the activity of MAO at FHC revealed a significant decrease in the activity of the enzyme in all examined groups in relation to the control group (table. No. 2). In the control group, MAO activity was 0.07 0.001 U / ex. In group II, MAO activity was 0.05 0.003 U / ex., Which is 28.6% lower than the control (p <0.001). In group III, there is a significant decrease in enzyme activity by 42.9% in relation to the control group and amounted to 0.04 0.004 U / ex. (p <0.001).

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

Table 2: Daily excretion of CA and MAO activity in apparently healthy subjects and patients with FHC, P <0.001

Group	A, µg / day	ON, µg / day	Yes µg / day	DOPA, µg / day	MAO, units / 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- SGHS without ischemic heart disease				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- SGHS with ischemic heart disease				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		

In our study, indicators of nonspecific inflammation were assessed in patients with ACS - cytokines: IL-6, IL-10, TNF-α and hs-CRP.

Table 3: Indicators of cytokines IL-6 and IL-10 in blood serum in patients with FHC without coronary artery disease

Indicators	Patient groups		
	SGHS without ischemic heart disease (n=56)	Control (n=15)	P
IL-6 (pg / ml)	15,3±2,1	8,5±0,9	<0,001
IL-10 (pg / ml)	8,4±0,4	8,2±0,7	>0,05

Table 4: Indicators of cytokines IL-6 and IL-10 in the blood serum of patients SGHS with ischemic heart disease

Indicators	Patient groups		
	SGHS with ischemic heart disease (n=98)	Control (n=15)	P
IL-6 (pg / ml)	24,5±0,9	8,5±0,9	<0,001
IL-10 (pg / ml)	8,1±0,7	8,2±0,7	>0,05

A study of TNF-α and hs-CRP in patients with FHC without and with coronary artery disease was carried out. Comparative assessment of TNF-α and hf-CRP parameters in blood serum in healthy people and in patients with FHC without clinical signs of coronary artery disease showed that in patients with FHC, the levels of TNF-a and CRP were 13.4 ± 2.2 and 2.7 ± 0, 1 which, respectively, is 1.76 times ($p < 0.001$) and 2.5 times ($p < 0.001$) more than control indicators (Table 5). Such tendencies are more pronounced in the group of patients with FHC with clinical signs of coronary artery disease (Table 5). Thus, the level of TNF-α in patients averaged 18.5 ± 1.8, which is 2.4 times higher ($p < 0.001$) than control indicators, and the average value of hf-CRP was 3.8 ± 0.1 mg / ml , which is 3.45 times higher ($p < 0.001$) than control indicators.

Table 5: Serum TNF-α and hf-CRP indices in patients with FHC

Indicators	Groups of examined persons			
	SGHS without ischemic heart disease (n=56)	SGHS with ischemic heart disease (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 coronary artery disease, its relationship with the characteristics 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). The 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 SAS activity in familial hypercholesterolemia can be regarded as compensatory, providing the mobilization of the body's defenses, an increase in the energy supply of the myocardium. A further increase in the tension of the SAS 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 appear, and a further increase in the activity of which becomes one of the main elements of the formation of ischemic heart disease and its complications. The results of the conducted studies have shown that with FHC there is a moderate activation of SAS associated with an increase in the excretion of catecholamines: A, HA, DOPA in 1.27; 1.14; 1.05 times, respectively ($p < 0.001$), YES 1.09 times ($p < 0.05$) in relation to healthy subjects. These data coincide with the data of L.M. Doborzhiginidze, N.A. Gratsiansky et al., A.I. Nesterova (2000). In turn, with FHC in patients with chronic forms of ischemic heart disease, there is an equivalent decrease in the daily excretion of catecholamines: A, HA, DA in 1.38; 1.41; 1.96 times, respectively ($p < 0.001$), DOPA - 1.28 times ($p < 0.05$) in relation to the control. In patients with CHS with the presence of chronic forms of coronary artery disease, inhibition of the SAS activity is manifested by a decrease in the hormonal and mediator link, and there is also 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 impaired microcirculation (10). From this point of view, it was especially interesting to study LPO processes in FHC, since the main biochemical indicator of blood is an increase in LDL. It has been established that in CHD and atherosclerosis there is an increase in LPO. The intensity of LPO reflects the degree of metabolic disorders in the body (8). Our results indicate an increase in lipid peroxidation processes in FHC without ischemic heart disease by 1.72 times (p <0.001), and the most pronounced intensification of lipid peroxidation processes is observed in chronic forms of ischemic heart disease, exceeding the control indicators by 2.16 times (p <0.001).

As is known, under conditions of lipid peroxidation, the key enzyme for the oxidation of biogenic amines, MAO, can undergo a significant transformation of its catalytic properties, as a result of which its activity towards monoamines decreases (7). We have studied the activity of MAO in healthy and patients with FHC with ischemic heart disease and without clinical manifestations of ischemic heart disease, during the observation it was revealed that the functional activity of MAO undergoes significant changes depending on the degree of manifestation of cardiovascular pathology. Thus, in patients with FHC without clinical forms of coronary artery disease, there is a decrease in MAO activity by 1.4 times (p <0.001). And in patients with CGHS with CHHD, the least activity of the enzyme is noted, which is 1.75 times (p <0.001) lower than the indicators of the control group, which confirms the qualitative violation of its catalytic properties.

The results obtained indicate that in patients with familial hypercholesterolemia, there is a highly reliable, strong positive relationship between A and HA with the level of IL-6 cytokine (r = 0.97 and r = 0.94; p <0.01) and IL-10 cytokine. (r = 0.93 and r = 0.94; p <0.01). Consequently, cytokines are undoubtedly the leading factors in the disruption of SAS activity, including in FHC .

Conclusion

1. A comprehensive study of individuals with FHC without clinical manifestations of coronary artery disease showed an increase in the excretion of adrenaline, norepinephrine, dopamine, DOPA by 26.5%, 14.4%, 9.3%, 4.5%, respectively, in relation to healthy activation of the hormonal link of the SAS, in connection with which its early correction is necessary to prevent the development of coronary artery disease.
2. A comprehensive study of FHC patients with chronic forms of ischemic heart disease revealed a decrease in the excretion of adrenaline, norepinephrine, dopamine, DOPA by 27.7%, 29.3%, 48.8%, 22.0%, respectively, in relation to the control group, indicating a decrease activity of the hormonal, mediator link and reserve capabilities of the SAS.
3. In subjects with CGHS, there is a significant decrease in the activity of MAO in relation to healthy subjects, which indicates a qualitative change in the catalytic properties of the enzyme.
4. In patients with familial hypercholesterolemia, a highly reliable, strong positive relationship between A and HA with the level of IL-6 cytokine (r = 0.97 and r = 0.94; p <0.01) and IL-10 cytokine (r = 0.93 and r = 0.94; p <0.01).
5. Comparative assessment of TNF-α and hf-CRP parameters in blood serum in healthy people and patients with CGHS without clinical signs of coronary artery disease showed that in patients with FHC, the levels of TNF-α and CRP were 13.4 ± 2.2 and 2.7 ± 0.1, which, respectively, is 1.76

times (p <0.001) and 2.5 times (p <0.001) more than control indicators, more pronounced changes are observed in the group of patients with FHC with clinical signs of coronary artery disease.

REFERENCES

1. Ezhov M.V., et al. Sergienko I.V., Rozhkova T.A., Kukharchuk V.V., Konovalov G.A., I. Russian guidelines for the diagnosis and treatment of familial hypercholesterolemia // Eurasian Journal of Cardiology. 2017. No. 2. p. 7–12.
2. Ezhov M. V., Bliznyuk S. A. Register of patients with familial hypercholesterolemia and patients of very high cardiovascular risk with insufficient effectiveness of lipid-lowering therapy (RENAISSANCE) Eurasian Cardiology Journal. 2019; No. 24-5, pp. 7-13.
3. Meshkov A.N., Stambolsky A.V., Nikitina L.N. et al. Genetic risk factors for the development of coronary heart disease in patients with familial hypercholesterolemia. Cardiology 2005; 7: 10-15.
4. Kees Hovingh G., Davidson M.H., Kastelein J.P., O'Konor A.M. Diagnosis and treatment of familial hypercholesterolaemia. European Heart Journal. 2013. No. 34.R. 962-971. DOI: 10.1093 / eurheartj / eht015.
5. Singh S., Bittner V. Familial hypercholesterolemia-epidemiology, diagnosis, and screening. Curr Atheroscler Rep. 2015.No.17 (2). P. 482. DOI: 10.1007 / s11883-014-0482-5.
6. Michael D.S., Sergio F. Taking a look under the hood. Journal of Clinical Lipidology. 2018. No. 5. P. 3–6. DOI: 10.1016 / j.jacl.2018.05.020
7. Schwartz J., Padmanabhan A. Aqui N., Balogun R. A., Delaney M., Dunbar N. M., Witt V., Wu Y., Shaz B. H. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J. Clin Apher. 2016 Jun; 31 (3): 149–62. DOI: 10.1002 / jca.21470.
8. Kees Hovingh G., Davidson M.H., Kastelein J.P., O'Konor A.M. Diagnosis and treatment offamilial hypercholesterolaemia. European Heart Journal. 2013. No. 34.R. 962-971. DOI: 10.1093 / eurheartj / eht015.
9. Lankin V.Z., Vikhkhert A.M., Tihaze A.K. Free radical processes in diseases of the cardiovascular system. Cardiology 2000; 7: 48-61
10. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017; 376 (18): 1713-22. doi: 10.1056 / NEJMoa1615664