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Immune-Mediated Inflammation of Coronary Heart Disease in Patients with Psycho-Emotional Disorders

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Abstract: Coronary heart disease (CHD) involves the development of severe coronary atherosclerosis and subsequent decrease in blood flow to the heart. Traditional risk factors such as smoking, diabetes, hypercholesterolemia and systemic hypertension are involved in the pathogenesis of CHD. However, 40-60% of cases of predisposition to CHD are hereditary, so it is generally believed that CHD is the result of both genetic predisposition and traditional risk factors [1,4,6]. In the Framingham Heart Study, a family history of CHD was defined as heart disease in immediate family members under age 60 in men or age 65 in women and was a powerful predictor of CHD [2,7,10]. Approximately one-third of patients with CHD have a family history of CHD, and individuals with a family history of CHD are approximately 1.5 times more likely to have a lifetime history of CHD than individuals without a family history [3,5,7].

Keywords: coronary heart disease, hypercholesterolemia, atherosclerosis, psych emotional status.

Introduction: Coronary heart disease refers to a complex clinical condition that includes a spectrum of conditions, including unstable angina, ST-segment elevation myocardial infarction (STEMI) and myocardial infarction without ST-segment elevation (STEMI). Accumulating evidence suggests the involvement of the inflammatory process in the pathogenesis of CHD, involving local immune cells in the coronary arteries, which generate inflammatory factors contributing to thrombus formation [1, 2]. Although nonatherosclerotic factors can also contribute to CHD, the most frequent cause of CHD is rupture or erosion of atherosclerotic plaques followed by thrombus formation. Nearly 60% of patients with CHD have high levels of high-sensitivity C-reactive protein (hsCRP) (>2.0 mg/L), a biomarker of systemic inflammation and a prognostic factor for high cardiovascular mortality, which is defined as a residual inflammatory process[3,11,13]. Atherosclerosis has been recognized as a chronic inflammatory disease characterized by dysfunctional immune inflammation involving interactions between immune cells (macrophages, T lymphocytes, and monocytes) and vascular cells (endothelial cells, smooth muscle cells) [4,28,29,32,33].

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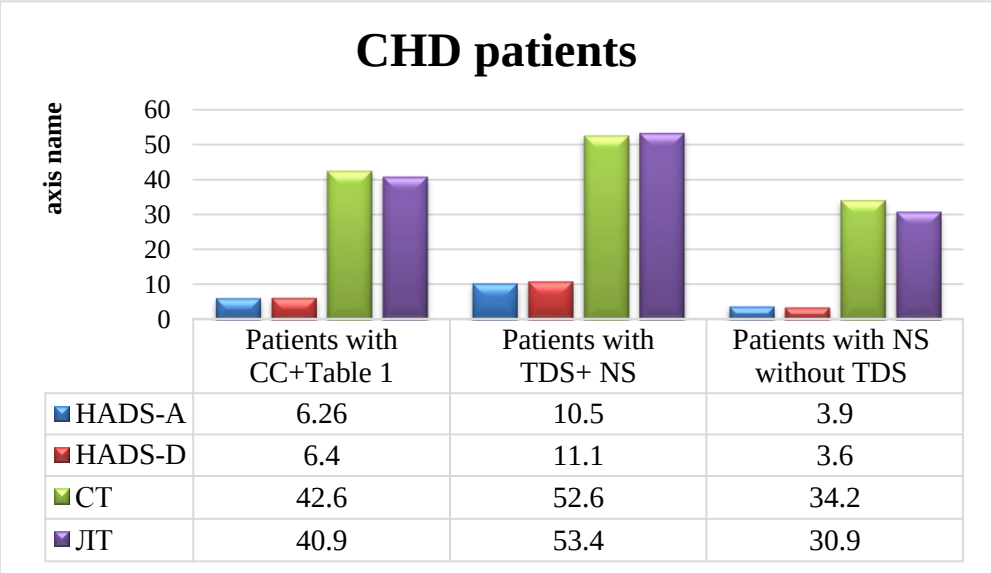
interactions between immune cells (macrophages, T lymphocytes, and monocytes) and vascular cells (endothelial cells, smooth muscle cells) [4,28,29,32,33].

Purpose of the study: evaluation of psychoemotional status in patients with unstable variants of angina pectoris.

Materials and methods of research: we decided to study the presence of TDS using two scales: Hospital HADS scale [Kozlova S.N. 2013]; Spielberger-Hanin scale [Psychiatry - Hoffman A.G. 2010], developed by Spielberger C.D. and adapted by Khanin Y.L. [Psychiatry - Hoffman A.G. 2010].

When testing with the above scales, we determined that 122 patients with NS had an anxiety-depressive syndrome.

The study showed that patients with NS had significantly high values for all parameters of the abovementioned scales (Fig.1). The hospital scale among patients with stable angina had the following mean values: HADS-D 6.43±0.35 and HADS-A 6.17, while patients with NS were statistically higher and had HADS-D 9.0±0.5 and HADS-A 9.5±0.52. But of particular attention is the mean value of these scores among patients with NS and TDS, HADS-D-11.1±0.61 points and HADS-A 10.6±0.58 points, respectively.



	Patients with CC+Table 1	Patients with TDS+ NS	Patients with NS without TDS
HADS-A	6.26	10.5	3.9
HADS-D	6.4	11.1	3.6
CT	42.6	52.6	34.2
ЛТ	40.9	53.4	30.9

Note: *HADS-D-depression, HADS-A-anxiety, ST-situational anxiety, LT-personal anxiety.*

Figure 1. HADS and Spielberger-Hanin Hospital Scale scores among CHD patients

When interviewing patients on the Spielberger-Hanin scale, there was an identical picture. Among patients with SS, the situational anxiety (SA) score was 42.55±2.3 and the personality anxiety (PA) score was 40.86±2.24; among patients with NS, the SA score was 49.1±2.7 and the PA score was 47.7±2.6; and among patients with NS and TDS, the scores were 52.6±2.9 and 53.4±2.93 respectively.

The study revealed that TDS was more frequent among females. Anxiety-depression syndrome severity scores were statistically indistinguishable in both groups.

Table 1. HADS and Spielberger-Hanin Hospital Scale scores among patients with NS and TDS depending on gender

Indicators	women (n=65)	men (n=57)	P-value
HADS-D (балл)	11,0±0,6	11,1±0,7	>0,5
HADS-A(балл)	10,5±0,4	10,6±0,6	>0,5
ST(grade)	53,6±2,8	53±2,4	>0,5
LT(grade)	53,5±3,1	52,1±2,9	>0,5

Note: *HADS-D-depression, HADS-A-anxiety, ST-situational anxiety, LT-personal anxiety*

ECG and ECHOG parameters were studied to compare cardiac parameters of patients with and without HC with and without TDS.

From Table 2 we can see that, among patients with NS, LVEF was statistically decreased than in patients with SS. In patients with NS and TDS, LVEF was insignificantly decreased than in NS patients without TDS. And also cases with ST-segment depression were 39% more frequent in patients with NS and TDS, in contrast to patients without TDS.

The above data indicate that comorbid conditions as psychosomatic disorders lead to destabilization of CHD, in turn, destabilized variants of CHD can increase the frequency of cases with fatal outcome.

HADS and Spielberger-Hanin scales among patients with NS show the presence of TDS in 78.1% of patients, which may explain the frequent cases with ST-segment elevation/depression and T-wave inversion. It should also be emphasized that TDS was 6% more frequent among females, although mean values of HADS and Spielberger-Hanin scales in both men and women were not statistically different, which explains frequent cases of CHD destabilization among women.

There were 202 patients with CHD under observation. Among them, 102 women and 100 men, mean age was 63.75 ± 11.37 years.

Results: Among these patients, arterial hypertension occurred in 140 patients (69.3%), DM in 44 patients (21.8%), 52 patients (25.7%) had a previous MI, rhythm disturbance was noted in 29 (14.35%), anemia in 33 (16.3%), previous stroke in 10 (5.0%), COPD in 11 (5.4%), obesity in 97 (48.1%), other diseases in 27 (13.36%).

In our study, the equivalent of angina in 19 (9.26%) patients was a bout of dyspnea. Twenty-six (12.68%) patients with NS had an atypical nature of the pain syndrome.

For general clinical tasks, patients were conventionally divided into 2 groups due to two scales (hospital HADS scale and Spielberger-Hanin scale): Group 1 patients comorbid with anxiety-depressive syndrome (n=122) and Group 2 patients without anxiety-depressive syndrome (n=33).

The indices of biochemical studies between NS patients with and without TDS, as well as between the comparable group of patients with SS are statistically insignificant, but we should emphasize the fact that among the patients with TDS the level of MC was higher by 104.5 μmol/l than in those without TDS.

After identifying the elevated blood MC level in patients with NS with TDS, we decided to study the peculiarities of blood lipid profile in patients with unstable angina pectoris, as well as the relationship between MC level and TDS.

Note. *^#- Significantly compared NS with and without TDS and with stable angina (* -P1<0.05, ** - P1<0.01, *** - P1<0.001, ^ -P2<0.05, ^^ - P2<0.01, ^^^ - P2<0.001, # P3<0.05, ## - P<0.01, ### - P<0.001). P1, P2, P3 - reliability of differences between 1gr and 2gr, 1gr and 3gr and 2gr and 3gr, respectively.

Analysis of the study results showed that among patients with NS and TDS, the values of CHC and LDL cholesterol were statistically significantly higher compared with patients with NS and without TDS, as well as with patients with SS. Atherogenicity coefficient was statistically elevated in all groups of patients, whereas the optimal value is considered to be when CA is 2-3. But these values were significantly higher among patients with NS and TDS. In addition, the level of MC also differed statistically among these groups, which shows the association of hyperuricemia with dyslipidemia. As we know, one of the objectives of the present study is to study serum levels of TNF-α, IL-1β, IL-4 and IL-10 cytokines in patients with NS with TDS (group 1) and NS without TDS (group 2), as well as to analyze the relationship with the MC level in blood. The results of determination of proinflammatory cytokines TNF-α, IL-1β pg/mL in NS patients with and without TDS indicate its statistically significant increase compared to the group with SS. In the group with unstable angina the level of TNF-α and IL-1β was significantly higher than in the group with stable angina (P<0.05).

Table 2. TNF-α, IL-1β, IL-4 and IL-10 levels in CHD patients with and without TDS (stable and unstable angina)

Indicator	SS (n=47)	1 group (n=122)	Group 2 (n=33)	P-value	
TNF-α pg/ml	66,3±2,2	72,2±2,3	66,2±2,1	>0,1	P1
				>0,5	P2
				<0,05	P3
IL-1β pg/ml	90,9±2,8	99,6±3,6	88,5±3,7	<0,05	P1
				>0,5	P2
				<0,05	P3
IL-4 pg/ml	22,4±0,9	20,3±0,7	23,0±0,9	>0,1	P1
				>0,5	P2
				<0,02	P3
IL-10 pg/ml	13±0,5	12,2±0,5	14,2±0,6	>0,2	P1
				>0,1	P2
				<0,01	P3
MK μmol/l	351,6±11,3	452,7±18	348,2±10,7	<0,001	P1
				>0,5	P2
				<0,001	P3

P1, P2, P3 - reliability of differences between CC and 1gr, CC and 2gr, 1gr and 2gr, respectively.

The indices of anti-inflammatory cytokines as IL-4 and IL-10 statistically differed (P1<0.01) between patients with TDS and patients without TDS and were as follows: patients with TDS and TDS -20.3 pg/ml and 12.2 pg/ml; patients without TDS - 23.0 pg/ml and 14.2 pg/ml respectively; with SS IL-4 and IL-10 - 22.4 pg/ml and 13.0 pg/ml respectively.

When studying the correlation between pro-inflammatory interleukin IL-1β and TDS parameters (Fig.3.3.1), there was a medium correlation between them (R^2 = 0,6134). When studying the relationship between the sum of TDS indices and TNF-α, a medium strength correlation (R^2 = 0.5799) was also revealed.

Considering the revealed peculiarity in MC level and its frequency among NS patients, we analyzed the mutual relations of cytokine balance and psychosomatic state depending on MC content in blood. The correlation between MC and proinflammatory IL-1β, TNF-α cytokines is strong (R^2 = 0.7894, R^2 = 0.7662 respectively).

Table 3. Indices of interleukin TNF-α, IL-1β, IL-4 and IL-10 in CHD patients (stable and unstable angina pectoris) depending on MC level among NS patients with TDS.

Indicators	NS + TDS (n=122)		CC (n=47)	P-value	
	Patients with elevated (≥360 μmol/L) MC, n=78	Patients with normal MC levels (≤360 μmol/L), n=44			
TNF-α pg/ml	103,3±4,6	93,1±3	90,9±3,7	>0,1 <0,05 >0,5	P1 P2 P3
IL-1β pg/ml	74,3±3,4	68,5±2,5	66,3±2,8	>0,2 >0,1 >0,5	P1 P2 P3
IL-4 pg/ml	19,8±0,9	21,2±0,9	22,3±0,9	>0,2 >0,1 >0,5	P1 P2 P3
IL-10 pg/ml	11,7±0,4	13,0±0,6	13,4±0,6	>0,1 <0,02 >0,5	P1 P2 P3
MK μmol/l	538,2±23,4	301,2±11,4	351,6±15,6	<0,001 <0,001 <0,01	P1 P2 P3

Note: *^# - differences relative to the data of the compared group are significant (* - P1<0.05, ** - P1<0.01, *** - P1<0.001, ^ - P2<0.05, ^^ - P2<0.01, ^^^ - P2<0.001, # - P3<0.05, ## - P3<0.01, ##- P3<0.001)

Among NS patients with TDS and elevated MC levels one can also see elevated values of proinflammatory cytokines as well as statistically significant MC levels in contrast to NS patients without TDS and SSs. (P<0,001).

Table 4. Indices of interleukin TNF-α, IL-1β, IL-4 and IL-10 in CHD patients (stable and unstable angina pectoris) depending on MC level among NS patients with and without TDS

Indicators	NS without TDS	NS + TDS	SS (n=47)	P-value	
	Patients with elevated (≥360 µmol/L) MC, n=10	Patients with elevated (≥360 µmol/L) MC, n=78			
TNF-α pg/ml	98,4±3,6	103,3±4,1	90,9±3,0	>0,5 >0,1 <0,02	P1 P2 P3
IL-1β pg/ml	73,8±2,9	74,3±2,8	66,3±2,1^	>0,5 <0,05 <0,02	P1 P2 P3
IL-4 pg/ml	23,7±1,0***	19,8±0,7#	22,3±0,9	<0,001 >0,2 <0,05	P1 P2 P3
IL-10 pg/ml	14,6±0,5***	11,7±0,5#	13,4±0,6	<0,001 >0,1 <0,05	P1 P2 P3
MK µmol/l	424,4±15,5***	538,2±23,4###	351,6±13,5^^^	<0,001 <0,001 <0,001	P1 P2 P3

Note: *# - differences relative to the data of the compared group are significant (* - P1<0.05, ** - P1<0.01, *** - P1<0.001, ^ - P2 <0.05, ^^^ - P2<0.01, ^^^ - P2<0.001, # - P3<0.05, ## - P3<0.01, ### - P3<0.001)*

Table 5. Indices of interleukin TNF-α, IL-1β, IL-4 and IL-10 in CHD patients (stable and unstable angina pectoris) depending on MC level among patients with NS without and without TDS.

Indicators	НС без ТДС (n=33)		SS (n=47	P-value	
	Patients with elevated (≥360 µmol/L) MC, n=10	Patients with normal MC levels (≤360 µmol/L), n=23			
TNF-α pg/ml	84,2±3,5**	98,4±3,4	90,9±3,1	<0,01 >0,2 >0,1	P1 P2 P3
IL-1β pg/ml	62,9±2,2***	73,8±2,7#	66,3±2,8	<0,001 >0,5 <0,05	P1 P2 P3
IL-4 pg/ml	22,7±0,8	23,7±1,1	22,3±0,8	>0,5 >0,5 >0,2	P1 P2 P3
IL-10 pg/ml	13,9±0,6	14,6±0,6	13,4±0,5	>0,5 >0,5	P1 P2

				>0,1	P3
MK, μmol/l	315,0±12,3	424,4±16,3	351,6±14,9	<0,001 <0,05 <0,001	P1 P2 P3

Note: *# - differences relative to the data of the compared group are significant (* - P1<0.05, ** - P1<0.01, *** - P1<0.001, ^ - P2 <0.05, ^^^ - P2<0.01, ^^^ - P2<0.001, # - P3<0.05, ## - P3<0.01, ### - P3<0.001)*

Conclusions: Thus, among patients with stable and unstable angina associated with BSU the indices of proinflammatory cytokines TNF-α, IL-1β were statistically significant (P<0.001). And also the indices of anti-inflammatory cytokines IL-4 and IL-10 were slightly decreased among NS patients with TDS, which shows a disturbance of cytokine balance, in particular among this category of patients. But the indices of anti-inflammatory cytokines IL-4 and IL-10 among NS patients without TDS did not differ significantly from those in the group of patients with stable angina pectoris.

Thus, the results of the study showed that in patients with NS with TDS there is a medium correlation between proinflammatory cytokines TNF-α and interleukin IL-1β and TDS indices (R^2 = 0.5799, R^2 = 0.6134). The correlation between MC and proinflammatory IL-1β, TNF-α cytokines was strong (R^2 = 0.7894, R^2 = 0.7662, respectively), showing a direct association of cytokine imbalance with increased MC levels in blood.

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