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Cardiometabolic risk factors and their relationship with the interleukin-6 receptor gene polymorphism (rs2228145) in patients with hypertrophic cardiomyopathy

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Aim. To analyze associations of interleukin-6 receptor gene (*IL6R*) polymorphism (rs2228145) with the clinical course characteristics of hypertrophic cardiomyopathy (HCM) in groups of patients with various cardiometabolic risk factors.
Material and methods. The sample consisted of 123 patients with HCM. The age of the included patients ranged from 18 to 91 years (59 [41; 66,5]), of whom 59 were men, 64 — women. Two age groups were identified: the first group included patients from 18 to 44 years old, the second — 45 years and older. The control group consisted of 200 people without cardiovascular diseases and other severe comorbidities.
For genetic testing, DNA was isolated from peripheral blood lymphocytes. Genotyping of the *IL6R* gene polymorphism (rs2228145) was carried out by real-time polymerase chain reaction.
Results. A significant prevalence of CC genotype of the *IL6R* gene polymorphism (rs2228145) was revealed in patients aged ≥45 years compared with the control group, which occurred in 14,1% and 3,0% of cases, respectively (CC:AC+AA, odds ratio (OR), 0,885, 95% confidence interval (CI), 1,051-0,691, p=0,006), and insignificant prevalence of C allele in this group, which does not reach the level of significance (A:C, OR, 0,870, 95% CI, 0,427-1,02, p=0,06). The prevalence of CC genotype (15,1% vs 3,0%) and C allele (39,0% vs 29,0%) was revealed in patients with HCM in combination with hypertension (HTN) compared with the control group (CC:AS+AA, OR=0,174, 95% CI, 0,047-0,650), p=0,004); (A:C, OR=0,638, 95% CI, 0,406-1,002), p=0,05).
Conclusion. The relationship between the *IL6R* gene polymorphism (rs2228145) and HTN in patients with HCM was confirmed. The presence of CC genotype and C allele of the rs2228145 polymorphism is significantly more common in patients with HCM with the disease onset ≥45 years of age. The presence of CC genotype and C allele of the *IL6R* gene polymorphism (rs2228145) is associated with HTN in patients with HCM.

Key words: hypertrophic cardiomyopathy, interleukin-6, interleukin-6 receptor gene, hypertension.

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Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease with an autosomal dominant manner of inheritance without a clear geographical, ethnic and sex distribution structure, which can manifest at any age [1]. In recent years, HCM pathogenesis are considered from the standpoint of the contribution of unmodifiable determinants (causal mutations, age, sex) and potentially modifiable factors (comorbidity). According to the meta-analysis reported by Finnochiaro G, et al. (2017), the debut and features of HCM in adults under 45 years of age is largely determined by causal genetic variants, severe myocardial hypertrophy (hypertrophy >3 cm) and a high risk of sudden death [2]. At the same time, the onset of the disease in older age groups often occurs under the influence of comorbidities, especially cardiometabolic risk factors, the frequency of which significantly increases with age [3]. Features of HCM course in older age groups are also associated with the presence of coronary artery disease in patients, the debut of which falls at this age [3, 4]. The urgency of comorbidity in older patients with HCM is specified by the high frequency of hypertension (HTN) and obesity [5-8]. According to Olivotto I, et al. (2013), only 25% of patients with HCM had normal body weight, 38% — overweight, 37% — OB, 27% — HET, 5% — type 2 diabetes (T2D) [5]. There are studies on the influence of obesity on myocardial remodeling in HCM [9, 10].

The importance of systemic inflammation in the pathogenesis of metabolic syndrome (MS) and its components has now been demonstrated in many studies [11-14]. The role of serum cytokines, in particular interleukin-6 (IL-6), has been shown in the pathogenesis of various cardiovascular diseases [15-20]. Thus, in the study by Buzas K, et al. (2004) revealed an increase in the concentration of IL-6 and soluble IL-6 receptor in the blood of patients with HCM [21].

IL-6 is one of the proteins of paracrine signaling, which is secreted during inflammation and has a diverse action, participating not only in inflammation, but also in the regulation of the endocrine functions and metabolism [22]. The broad spectrum of action of IL-6 is due to its transmembrane receptors, which are located in most body tissues: myocardium, spleen, kidneys, lungs, liver and brain. IL-6 receptors are not directly involved in signal transduction, but they provide homodimerization of another transmembrane receptor (gp130), which triggers the intracellular signaling [22]. The IL-6 receptor also exists in a soluble form and is the extracellular domain of the membrane receptor. Through the effects of soluble IL-6 receptor, gp130 is activated even in those cells that do not have the membrane IL-6 receptor [23]. In particular, IL-6 can cause myocardial hypertrophy by acting on gp130, despite the fact that there are no IL-6 receptors in cardiomyocytes [24].

Compared with studies concerning the plasma IL-6 level, papers devoted to polymorphism of IL6 receptor (*IL6R*) gene and their relationship with clinical and paraclinical parameters are much less common in the literature and concern mainly coronary artery disease [25-27]. A few works on the frequency of polymorphic variants of the *IL6R* gene are devoted to MS [28, 29], HTN [30], dyslipidemia [31, 32] and aortic stenosis [33]. The distribution of the polymorphic variant rs2228145 of the *IL6R* gene and its relationship with the manifestations of HCM are practically not studied to date. The aim of this study was to study the association of *IL6R* gene polymorphism rs2228145 with the clinical course of HCM.

Material and methods

The study group consisted of 123 patients with HCM. The diagnosis was made based on the 2014 ESC guidelines on diagnosis and management of HCM [1]. The age of the patients included in the study ranged from 18 to 91 years (59 [41; 66.5]), There were 59 men and 64 women. Two age groups were identified: the first group included patients aged 18-44 years, the second — patients aged ⩾45 years. Criteria for HCM with concomitant hypertension were as follows:

1. Positive family history of HCM or sudden cardiac death (SCD) at a young age in first-degree relatives.

2. Discrepancy between severe left ventricular hypertrophy (maximum wall thickness ⩾15 mm) and recent mild to moderate HTN with adequate medical adherence, as well as the absence of other causes of left ventricular hypertrophy.

The control group consisted of 200 people without cardiovascular diseases and other severe comorbidities. All patients signed informed consent. For genetic testing, DNA was isolated from peripheral blood lymphocytes. Genotyping of *IL6R* gene polymorphism rs2228145 was carried out by real-time polymerase chain reaction.

Statistical processing was carried out using Microsoft Excel 2010, IBM SPSS and Jamovi packages. Normal distributed data were presented as mean ± standard deviation. Non-normally distributed data are presented as median and quartiles. For analysis of relationship of qualitative variables, contingency tables were constructed. To compare frequencies, we used the Pearson's chi-squared test. If the expected frequency in contingency tables was <5, then the exact test was used. For contingency tables 2x2 with a small number of objects (up to 40-50), the chi-

Table 1
Clinical characteristics of patients with HCM, the incidence of comorbidities and cardiometabolic risk factors

Parameter	HCM (n=123), n (%)
Sex	
Male	59 (48%)
Female	64 (52%)
Age	
<45 years old	38 (30,9%)
⩾45 years old	85 (69,1%)
Class I-II HF	88 (71,5%)
Class III-IV HF	35 (28,5%)
Atrial fibrillation	31 (25,2%)
Ventricular tachycardia	7 (5,7%)
Grade V ventricular premature beats	16 (13,0%)
Blocks	
Atrioventricular block	1 (0,8%)
Sinoatrial block	4 (3,3%)
LVOTO	49 (39,8%)
SCD	3 (2,4%)
Hypertension	73 (59,3%)
Obesity (BMI >30)	45 (36,6%)
Type 2 diabetes	24 (19,5%)

Abbreviations: LVOTO — left ventricular outflow tract obstruction, SCD — sudden cardiac death, HCM — hypertrophic cardiomyopathy, BMI — body mass index, HF — heart failure.

Table 2
Echocardiographic parameters in patients with HCM in different age groups

Parameter	<45 years (n=38) Me [25%;75%]	⩾45 years (n=85) Me [25%;75%]	p
Age, years	26 [18,5;39,8]	63 [58;72]	<0,001
IVS, mm	22 [19;25]	20 [18;22]	0,016
LVPW, mm	12 [10;17]	13 [11;15]	0,381
LA, mm	42,5 [38,3;50]	47 [43;52]	0,019
LA index	26 [22;29]	25 [23;28]	0,982
MMI	202 [153;259]	176 [150;215]	0,143
EDD, mm	42 [37;50]	48 [43;51]	0,015
EDD index	25 [20,5;27]	25 [23;28]	0,236
EF, %	64,5 [60;71,5]	63 [57;68]	0,194

Abbreviations: LVPW — left ventricular posterior wall at diastole, MII — myocardial mass index, EDD — end-diastolic dimension, LA — left atrium, IVS — interventricular septum at diastole, EF — ejection fraction.

squared test was used with a correction for continuity, and if its application were violated, Fisher's exact test was used. Differences were considered significant at p<0,05.

Results

Clinical characteristics of patients. The experimental group in the study consisted of patients with HCM aged 18 to 91 years (59 [41; 66.5]; men — 48%, women — 52%). The most frequent comorbidity was HTN, which occurred in 59,3% of cases and was recorded mainly in patients aged ⩾45 years (94,5%). HTN was observed in 81,2% of patients aged ⩾45 years, while among patients aged <45 years it was detected in 10,5% of cases (p<0,001). Obesity was detected in 50,6% of older patients and in 5,3% of patients in the younger age group (p<0,001). T2D was diagnosed in 27,1% of patients aged ⩾45 years and in 2,6% of patients aged <45 years (p=0,002). Atrial fibrillation occurred in 29,4% of patients in the older age group and in 2,6% of patients aged <45 years (p=0,108). Ventricular arrhythmias were detected in 10,5% of patients in the younger age group, while in the older age group they were detected in 3,5% (p=0,122). In young patients, atrioventricular block was detected in 2,6% of cases and sinoatrial block in 5,3%, while in the older age group they were 0% and 2,4%, respectively (p=0,223). Left ventricular outflow tract obstruction (LVOTO) was detected in half of young patients and in 35,3% of patients in the older age group. Thus, the presence of comorbidities, in particular cardiometabolic risk factors, is most typical for patients aged ⩾45 years. Young patients showed a predominance of arrhythmias and conduction disorders and a high incidence of obstructive HCM. SCD was recorded with approximately the same frequency in patients of both age groups (2,4% vs 2,6%).

The clinical characteristics of the patients included in the study are presented in Table 1.

The interventricular septal (IVS) thickness at diastole in patients with HTN ranged from 12 to 28 mm (20 [18; 22]) and did not statistically differ from that in non-HTN patients, in whom the IVS thickness varied from 13 to 45 mm (22 [18; 25]) (p=0,144). However, there was a significant thickening of the left ventricular posterior wall (LVPW) at diastole in HTN patients (13 [12; 16] and 11 [10; 16], p=0,029). The end-diastolic dimension (EDD) in patients with HTN was significantly greater than in non-HTN patients (49 [43; 52] and 44 [38; 49], p=0,004). The left atrial (LA) diameter was higher in patients with HCM and HTN compared to patients with HCM without HTN (47 [43; 53] and 44 [39,3; 50], p=0,007).

It should be taken into account that among patients with HCM there were isolated cases of

Table 3

Age characteristics of the distribution of genotypes and alleles of IL6R gene polymorphism rs2228145 in patients with HCM

	⩾45 years (n=85)	Control (n=200)	p
AA	32 (37,6%)	90 (45,0%)	0,021
AC	41 (48,2%)	104 (52,0%)	
CC	12 (14,1%)	6 (3,0%)	
A	105 (61,8%)	284 (71,0%)	0,06
C	65 (38,2%)	116 (29,0%)	

Table 4

Distribution of genotypes and alleles of IL6R gene polymorphism rs2228145 in the group of patients with HCM in combination with HTN and in the control group

	HCM and HNT (n=73)	Control (n=200)	P
AA	27 (37,0%)	90 (45,0%)	0,015
AC	35 (47,9%)	104 (52,0%)	
CC	11 (15,1%)	6 (3,0%)	
A	89 (61,0%)	284 (71,0%)	0,05
C	57 (39,0%)	116 (29,0%)	

Abbreviations: HTN — hypertension, HCM — hypertrophic cardiomyopathy.

Table 5

Distribution of genotypes and alleles of IL6R gene polymorphism rs2228145 in obese patients with HCM and in the control group

	HCM and obesity (n=45)	Control (n=200)	P
AA	18 (40,0%)	90 (45,0%)	0,058
AC	21 (46,7%)	104 (52,0%)	
CC	6 (13,3%)	6 (3,0%)	
	(n=90)	(n=200)	
A	57 (63,3%)	284 (71,0%)	0,193
C	33 (36,7%)	116 (29,0%)	

Abbreviation: HCM — hypertrophic cardiomyopathy.

dilated phase of the disease. In this case the diagnosis was verified based on a family history of HCM and confirmed by the presence of mutations in the genes of myocardial contractile proteins.

Patients with normal body weight were found to have more pronounced IVS hypertrophy compared with obese patients (21 [18,3; 25,0] and 20 [17; 21], respectively, p=0,042). On the contrary, there was a higher LVPW thickness (14 [12; 16] and 12 [10; 14], respectively, p<0,001) and LA diameter (48 [43; 54] and 46 [41.3; 50], respectively, p=0,037) in obese patients compared with patients with normal body weight.

It was found that the IVS thickness in the group of patients <45 years old prevails in comparison with the group of patients aged ⩾45 years (22 [19; 25] vs 20 [18; 22], p=0,016). In patients aged ⩾45 years, compared with patients aged <45 years, there was a higher LA diameter (47 [43; 52] and 42.5 [38,3; 50], respectively, p=0,019) and EDD (48 [43; 51] and 42 [37; 50], p=0,015). Obstructive HCM occurred in 35,3% of patients aged ⩾45 years and in half of patients aged <45 years (Table 2).

For obese patients with HTN, there were significantly higher values of LVPW thickness compared with patients with normal body weight and without HTN (145 [12,3; 16] and 11 [10; 15,8], respectively, p=0,002). There were higher LA diameter (47,5 [43; 53,8] vs 43 [39; 49,5], p=0,008) and EDD (48,5 [43,3; 52] vs 43,5 [38; 49], p=0,012) in patients with HTN and obesity compared with the group of non-obese patients without HTN.

Distribution of genotypes and alleles of the *IL6R* gene polymorphism rs2228145 in patients with HCM. A significant prevalence of the CC genotype was revealed in patients with HCM aged ⩾45 years compared with the control group, which occurred in 14,1% and 3,0% of cases, respectively (CC:AC+AA, odds ratio (OR), 0,885, 95% confidence interval (CI), 1,051-0,691, p=0,006). There was also prevalence of C allele in this group, which does not reach the level of significance (A:C, OR, 0,870, 95% CI, 0,427-1,02, p=0,06) (Table 3).

The prevalence of CC genotype (15,1% vs 3,0%) and C allele (39,0% vs 29,0%) was revealed in patients with HCM in combination with HTN compared with the control group (CC:AC+AA, OR=0,174, 95% CI, 0,047-0,650, p=0,004); (A:C, OR, 0,638, 95% CI, 0,406-1,002, p=0,05) (Table 4).

There were no significant differences in the distribution of genotypes and the occurrence of alleles of *IL6R* gene polymorphism rs2228145 in obese patients with HCM (Table 5).

There were no significant differences in echocardiography in patients with HCM, depending on the *IL6R* gene polymorphism rs2228145.

Discussion

The clinical course of the disease is significantly influenced by comorbidities, the incidence of which increases with age [3, 5-8, 34, 35]. In the experimental group of patients with HCM, the incidence of HTN, obesity, T2D, atrial fibrillation was higher

in patients with HCM in the older age group than in young patients, which is consistent with the data of most studies [5, 36]. The study by Ingles J, et al. (2017) and numerous other works revealed the higher prevalence HTN in older patients with non-familial HCM [3, 5-8, 34, 35, 37]. Age of onset is an important determinant of the clinical course of HCM [2, 38-41]. As a result of the study, we revealed an association of the CC genotype and C allele of *IL6R* gene polymorphism rs2228145 with HTN in patients with HCM with the onset of disease ⩾45 years. Our results are consistent with the work of LV Topchieva et al. (2020), which also revealed a relationship between the development of AH and the carriage of the CC genotype in the *IL6R* gene [30]. As you know, HTN is accompanied by an increase in proinflammatory cytokines in plasma and vascular tissues, including IL-6 [14]. In our work, no differences were found in the distribution of genotypes and alleles of the *IL6R* gene polymorphism rs2228145 in obese and non-obese patients. A reliable analysis of the distribution of genotypes and alleles in the group of obese patients with HCM and HTN was not possible due to the small the number of patients. However, Jiang CQ, et al. showed that in carriers of the AA genotype of the *IL6R* gene polymorphism rs2228145, MS was more common, despite a lower level of plasma IL-6. In white carriers of the same genotype, central obesity was more common and this phenomenon did not apply to Mongoloid people. At the same time, the CC genotype was associated with a higher level of IL-6, but this was not accompanied by a high incidence of HTN [29]. The role of serum IL-6 level and *IL6R* gene polymorphisms in the pathogenesis of HCM in patients with obesity and HTN requires further clarification. It is possible that this depends on the patient's age and are modulated by various components of MS.

Conclusion

The relationship between the *IL6R* gene polymorphism (rs2228145) and HTN in patients with HCM was confirmed. However, its influence on myocardial remodeling, hypertrophy, and LA parameters require additional studies involving a larger number of patients. The presence of CC genotype and C allele of the *IL6R* gene rs2228145 polymorphism is significantly more common in patients with HCM with the disease onset ⩾45 years of age. The presence of CC genotype and C allele of the *IL6R* gene polymorphism (rs2228145) is associated with HTN in patients with HCM. Further analysis of the relationship between serum IL-6 levels and polymorphic variants, as well as their effect on the clinical course of HCM in different age groups, requires further research.

Relationships and Activities: none.

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