Genotype-phenotype correlations in Polish patients with hypertrophic cardiomyopathy: Preliminary report

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is commonly defined by the presence of increased left ventricular (LV) wall thickness which cannot be explained by abnormal loading conditions such as arterial hypertension and/or aortic valve stenosis. The prevalence of HCM is 1:500, which makes it one of the most common genetic cardiological diseases [1]. According to the literature, the isolated form of HCM is most often caused by the occurrence of pathogenic variants in genes encoding sarcomere proteins. Until now around 1500 pathogenic variants in 11 genes encoding sarcomere proteins were identified [2]. In this report, we present the clinical characteristics and the results of genetic testing of HCM patients diagnosed and treated in the 3rd Department and Clinical Department of Cardiology, the Silesian Center for Heart Diseases.

METHODS

Forty-eight consecutive patients with HCM were recruited during their routine follow-up visit in the 3rd Department of Cardiology, the Silesian Center for Heart Diseases in Zabrze. Blood for biochemical analyses was collected after 8–10 hours of fasting; additionally, blood for genetic analyses was secured and stored in –80°C. The family history of each patient was collected in detail. Two patients were excluded because the diagnosis of HCM was negatively verified. The HCM sudden cardiac death risk score (HCM SCD risk score) was calculated for all patients [1]. Information regarding genetic and bioinformatics analysis is presented in Supplementary material.

Statistical analyses

Fisher's exact test was used for detection of differences between categorical variables, whilst the Kruskal-Wallis test was used for detection of differences between continuous variables. The Dunn test was used as a *post hoc* test for the Kruskal-Wallis test. Two-sided *P*-value <0.05 was considered statistically significant for all comparisons, except for the *post-hoc* test where the Bonferroni correction was used. Continuous variables were reported as medians and interquartile ranges, categorical variables were reported as counts and percentages. Statistical analyses were carried out in R software [3].

RESULTS AND DISCUSSION

We were able to identify the pathogenic/likely pathogenic variants associated with the occurrence of HCM in 15 (32.6%) patients. We have also found 16 additional variants that were classified as VUS (variant of uncertain significance). Interestingly 7 (44%) of those variants were predicted to have a significant damaging effect on coded protein by both SIFT and PolyPhen-2 prediction algorithms (PolyPhen-2 score ≥0.74 and Sift score ≤0.04).

Table 1. Clinical characteristics of the study population, and variants identified as disease-causing in the studied population

	Pathogenic/likely pathogenic variant positive (n = 15)	Variant of uncertain significance (n = 16)	No identified pathogenic/VUS variant (n = 15)	*P*-value
Age, years, median (IQR)	51 (37–59)	58 (46–68)	55 (40–65)	0.15
Male gender, n (%)	9 (60)	8 (50)	9 (60)	0.81
Heart failure, n (%)	9 (60)	9 (56)	7 (47)	0.81
Alcohol ablation or myectomy of IVS, n (%)	1 (7)	3 (19)	2 (13)	0.86
Implantable cardioverter defibrillation, n (%)	6 (40)	5 (33)	5 (33)	0.93
Atrial fibrillation, n (%)	6 (40)	6 (38)	2 (13)	0.23
Ventricular tachycardia, n (%)	7 (47)	5 (31)	4 (27)	0.54
HCM-SCD risk score, median (IQR)	5.7 (4.5–9.4)	3.4 (2.1–7.1)	3.7 (2.3–5.4)	0.15
NT-proBNP, pg/ml, median (IQR)	906 (177–1651)	657 (404–1025)	349 (139– 959)	0.25
Max. thickness of LV, mm, median (IQR)	20 (17.5–21)	19.5 (16–21.3)	18.0 (15.5–21)	0.55
LVOT Vmax (Valsalva), mm Hg, median (IQR)	9 (5–68)	15 (6–63)	22 (10–43)	0.73
Identified pathogenic/likely pathogenic variants (n = 15)				
Gene symbol	**Gene name**	**Identified variants**		
MYBPC3	Myosin-binding protein C	Transcript: NM_000256.3 c.3490+1G>T[a] (2), c.3697C>T[a], c.821+1G>A[a], c.3040delC[a], c.3407_3409delACT[b], c.2449C>T[b] (2×)		
MYH7	Myosin 7	Transcript: NM_000257.3 c.2555T>C[1], c.5135G>A[a], c.2011C>T[b]		
MYL3	Essential myosin light chain 3	Transcript: NM_000258.2 c.170C>G[b],		
TNNI3	Troponin I3	Transcript: NM_000363.5 c.407G>A[a]		
TNNT2	Troponin T	Transcript: NM_000364.3 c.311G>T[a]		
RYR2	Ryanodine receptor 2	Transcript: NM_001035.2 c.1069G>A[c]		

[a]Reported as pathogenic and/or likely pathogenic by multiple sources; [b]Reported as pathogenic and/or likely pathogenic and as VUS with *in-silico* analyses predicting damaging effect and/or functional studies; [c]Variant pathogenic for CPVT, we cannot exclude that this is not a causative variant of HCM. Dichotomous variables are presented as counts and percentages. Values are presented as the median and interquartile range (IQR)

Abbreviations: HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction, VUS, variant of uncertain significance

There were no significant differences in clinical characteristics between the groups. There was, however, a trend toward a higher HCM SCD risk score in patients with pathogenic/likely pathogenic variants (Table 1).

HCM is one of the most common cardiomyopathies. Despite this, only in 40%–60% of patients, it is possible to identify the variant responsible for the disease [1]. The reason why it is not possible to identify causative variants in a large proportion of patients may be due to the involvement of other genes not yet identified as associated with HCM. Oligo- or even polygenic inheritance may be another cause. In rare cases, copy number variations, microdeletions, as well as incorrect classification of myocardial hypertrophy as HCM, may be the reason [4, 5].

The most common pathogenic/likely pathogenic variants responsible for the occurrence of HCM in our population were identified in genes encoding proteins of the sarcomere, in particular, *MYBPC3* and *MYH7*. This is consistent with the results of genetic testing of HCM patients in other populations [2, 4]. Our data suggested a possible relationship between a higher risk of SCD assessed using the HCM SCD risk score [1, 6] in patients with a confirmed pathogenic variant. This may reflect observations from other cohorts that in patients with identified causative variant the disease tends to have a more aggressive course [5]. The frequency of alcohol ablation or surgical myectomy was similar in both groups. Similar results were reported by Loar et al. [5]. In general, genotype-phenotype correlations in patients with HCM are modest [7, 8]. Interestingly in one case, we found a variant in the *RYR2* gene pathogenic for catecholaminergic ventricular tachycardia (CPVT) and not HCM. We did not find any other variants in this patient in genes typically associated with HCM. This patient was burdened with recurrent ventricular arrhythmias and his HCM-SCD risk score was calculated to be 24.7. In literature, *RYR2* variants were reported as a possible rare cause of HCM [9, 10]. The pathogenic variant in this gene was also proved to be associated with the HCM phenotype in animal studies [11]. Nonetheless, this variant will be subjected to segregation analysis, and we will try to carry out whole-exome sequencing in this patient.

CONCLUSIONS

In the studied population, we identified variants that might be responsible for the phenotype in 33% of patients. Fur-

ther analysis is required to assess the potential pathogenicity of identified VUS found in 35% of cases.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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Ethical approval: The study was approved by the Bioethical Committee of the Medical University of Silesia (KNW/0022/KB1/102/18) and by the Bioethical Committee of the Chamber of Physicians (KBCz-0018/2015). The study was conducted according to the guidelines of the Declaration of Helsinki.

Conflict of interest: None declared.

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