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PhD Thesis Summary

INNOVATIVE RESEARCH ON GENETIC, CLINICAL AND PARACLINICAL CORRELATION IN THE MANAGEMENT OF PEDIATRIC PATIENTS WITH HYPERTROPHIC CARDIOMIOPATHY

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Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogeneous disorder in terms of clinical picture and evolution, affecting all age groups, from newborn to elderly. It represents the main cause of sudden death in young adults, this even being the first manifestation of the disease. At pediatric age, HCM represents the second most frequent cardiomyopathy, but there is little data on the prevalence of this disease among children. The knowledge of the epidemiological data of HCM in children and their systematic collection is extremely important, given the heterogeneity of this age group in terms of clinical and paraclinical evolution. In Romania, so far, there are no nationally reported data on the epidemiology of HCM in the pediatric age group. Data on establishing the prognosis and risk of sudden cardiac death (SCD) in the pediatric age group are less accurate compared to the adult class, evaluating the prognosis in children represents a challenge. Genetic consultation is extremely important for children with HCM. To date, there are few published studies on genetic testing in HCM in pediatric age, most of them being focused on studying sarcomere mutations, and are more limited to case reports, without a systematic assessment of the mutation's influence on the evolution and prognosis of this condition, which makes the data on the existence of an association between genetic etiology and prognosis in HCM in the pediatric population insufficient. Along with sarcomere mutations, several other factors, such as the polymorphisms of genes encoding the RAA system, may have an impact on CMH evolution and prognosis in children.

1st Study: Epidemiological features in hypertrophic cardiomyopathy in children

The first study of this PhD thesis is a prospective, observational study, the objective of which was to evaluate the epidemiological characteristics of children diagnosed and progressively evaluated with HCM at the Pediatric Cardiology Department from the Emergency Institute for Cardiovascular Diseases and Transplant, Târgu Mureș. This study reinforces the fact that HCM in the pediatric age group has a significant heterogeneity regarding age at diagnosis, etiological form, family history, symptomatology, clinical evolution. Most clinical forms are nonsyndromic, including family forms. Due to the uniqueness of this center at national level, a feature that derives from the high specialization and the continuity it offers in the diagnosis and treatment of pediatric cardiovascular diseases, as well as the fact that the addressability of this center is from all regions of our country, we can consider that pediatric patients diagnosed with hypertrophic cardiomyopathy and included in this study reflect the epidemiological profile of pediatric hypertrophic cardiomyopathy at the national level.

2nd Study: Clinical and paraclinical correlations in children with hypertrophic cardiomyopathy

HCM remains one of the most common causes of SCD in children and young adults. A better understanding of the relationship between etiology, phenotype and prognosis will facilitate the systematic study of risk factors for adverse events in the pediatric age group, with major implications in family counseling and

clinical management, resulting in improved morbidity and mortality. The second study in this PhD thesis proposed itself a comparative analysis regarding the clinical and paraclinical evolution of patients, based on the age of patients at time of diagnosis and the family history of HCM and / or SCD, and the identification of clinical-echocardiographic correlations respectively, in order to identify the echocardiographic parameters that can be used as prognostic factors, in order to improve the management of these patients. According to the results of this study, the clinical evolution of pediatric patients with HCM was not influenced by the small age at the time of diagnosis, but it was influenced by the positive family history for hypertrophic cardiomyopathy and / or SCD. The evolution of ECG and echocardiographic parameters was also significantly influenced by positive family history and less influenced by small age at the time of diagnosis. Following the analysis of the statistical correlations between the echocardiographic parameters and the classification of the patients in the NYHA / ROSS functional class, the echocardiographic parameter with the best prognostic value was found to be the gradient in the left ventricular ejection tract, which has a specificity of 73% and a sensitivity of 66 % in the prediction of functional class IV at 12 months from the moment of the first echocardiographic evaluation, the cut-off value calculated being 67mmHg.

3rd Study: Study of MYH7, MYBPC3 and ACE gene mutations and their role in establishing prognosis in pediatric patients with hypertrophic cardiomyopathy

To date, genetic testing in HCM in children has been the subject of only few studies, most of them being focused on the study of sarcomere gene mutations. The third objective of this study was to find out the genetic profile of children with HCM diagnosed and evaluated in the Pediatric Cardiology Department from Târgu Mureş, by evaluating the existence of mutations (deletion/duplication) of two of the most commonly involved genes in the etiology of sarcomere HCM (MYH7 and MYBPC3), and by studying the type I / D polymorphism of the ACE gene, and also to identify possible correlations between the presence / absence of the mutation, and between the genotype of the polymorphism and the progression of HCM. We identified no mutations in the MYH7 and MYBPC3 genes in the studied group. However, we should mention that, given the high costs involved by genetic testing in HCM, it was not possible to test the entire genetic panel involved in the etiology of this condition, so future studies are needed in this regard, in order to find out the sarcomeric genotype profile of children with HCM in Romania. In the present study, after testing the existence of a correlation between the clinical evolution of the patients (as objectified by the classification in the functional class) and the genotype for the polymorphism I/D of the ACE gene, we could not prove any influence of the genotype I / D on the clinical evolution; the results revealed that, in the case of the studied group, the clinical evolution was independent of the genotype of the polymorphism I / D of the ACE gene. By testing the existence of a correlation between the genotype of the polymorphism and the echocardiographic evolution of the patients (we followed echocardiographic parameters that quantify the severity of the left ventricular hypertrophy, parameters that evaluate the hemodynamic consequences of the left ventricular hypertrophy on the left ventricular outflow tract, echocardiographic parameters of the diastolic function), we found that the only echocardiographic parameter influenced by the genotype of ACE gene I/D polymorphism in this study was the Z score of the diastolic diameter of the posterior wall of the left ventricle. Thus, a statistically significant correlation ($p = 0.0417$) was found between the value of this parameter measured at baseline and the genotype of the ACE gene I/D polymorphism: a negative correlation for genotype II, and positive one for genotype DD and ID respectively, which means that the D allele is associated with a higher Z score of the posterior wall diameter at BL, thus with a more severe hypertrophy, compared with the I allele. D allele was also correlated with younger age at diagnosis, the median age being lower in patients with DD and ID genotype, compared to those with II genotype, but the difference was not statistically significant.

By studying the epidemiological profile of HCM in the pediatric age, the evaluation of history-clinical-paraclinical correlations in pediatric patients with HCM, the evaluation of sarcomere mutations and the role of ACE I / D polymorphisms in the evolution of pediatric patients with HCM, this PhD thesis contributes to the progress of research regarding HCM in the pediatric age group. More in-depth research concerning the impact that the genetic substrate has on the development and progression of HCM, and implicitly a better understanding of the genotype-phenotype relationship, knowledge of epidemiology, creation of risk prediction models for sudden cardiac death applicable to the pediatric age group, would improve the management of these patients, thus improving morbidity and mortality through HCM.