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RESEARCH ARTICLE

Comparison Between Clinical and Echocardiographic Findings in Infants and Children Diagnosed with Hypertrophic Cardiomyopathy

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Background: Hypertrophic cardiomyopathy is a rather common hereditary disease with an autozomal dominant character, caused by mutations of genes that code for proteins of the cardiac sarcomere. The observed prevalence of this disease is much lower in pediatric patients compared to adults, because it's late gene expression. Hypertrophic cardiomyopathy presenting in infancy has been shown to have a very high mortality. **Methods**: Thirty-nine patients diagnosed with hypertrophic cardiomyopathy in the IIIrd Pediatric Cardiology Department from Tîrgu Mureş were included in this study. Patients were divided into two groups: group 1 – patients diagnosed during infancy, group 2 – patients diagnosed after 1 year of age. Data regarding familial and personal history, and echocardiographic findings were compared between these two groups. **Results**: Group 1 included 17 patients and group 2 - 22 patients. Positive familial history was found in both groups (group 1 – 6 cases, group 2 – 3 cases), all of them in obstructive forms. Syncope was found in four cases, all of them in group 1 (p=0.02; odds ratio 15; 95% CI, 0.7473 to 301.1). While in group 1, asymmetric septal hypertrophy was predominant (64.7%), in group 2 – concentric left ventricular hypertrophy predominated (54.5%). Obstructive hypertrophic cardiomyopathy was found in 14 patients in group 1 (82.4%)compared to 13 patients in group 2 (59.1%). Diastolic function was impaired more predominantly in group 1 (p=0.0274; odds ratio 11.67; 95% CI, 1.526 to 89.17). **Conclusions**: hypertrophic cardiomyopathy has an extensive clinical variability with regard to age of onset, severity and progression of disease.

Keywords: hypertrophic, cardiomyopathy, infants, children

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Introduction

Hypertrophic cardiomyopathy (HCM) is a rather common hereditary disease with an autozomal dominant character, caused by mutations of genes that code for proteins of the cardiac sarcomere [1]. It affects the hearts of both children and adults. It has an estimated prevalence in the adult population of 1:500 [2,3]. The observedprevalence of this disease is much lower in pediatric patients compared to adults, because it's late gene expression [4]. HCM accounts for 42% of childhood cardiomyopathy and has an incidence of 0.47/100000 children [5].

Regardless of its etiology, the key phenotypic finding of the disease is an inappropriate ventricular hypertrophy [6], in the absence of hypertension and valve disease. HCM often occurs in families, with an identifiable inheritance pattern, but many sporadic cases are also identified [7]. Recent data classify two-thirds of children as having idiopathic disease [8].

Regarding the gender distribution, in one study the incidence of HCM was found to be 69% more common in males,and occurred at 10 times the rate in subjects under age 1 [5].

HCM has a heterogeneous clinical course and expression [9-11]. It is the most common cause of sudden cardiac death during exercise in childhood and adolescence [12,13], having a higher mortality (annual rate 4.6% to 5.8%) [14-16] than in adult life (1% to 4%) [17,18].

The risk factors for poor outcomes include young age, low weight, presence of congestive heart failure, lower left ventricular fractional shortening, or higher left ventricular end-diastolic posterior wall thickness or end-diastolic ventricular septal thickness at the time of cardiomyopathy diagnosis [19].

HCM presenting in infancy has been shown to have a very high mortality, of order of 50% within the first year [20]. In one study, in case of children diagnosed with HCM at younger than 1 year, the reported rate of death or transplantation was 21% (95% CI 16-27) at 2 years, [21].

Methods

Study patients

The database at the IIIrd Pediatric Cardiology Department from Institute of Cardiovascular Disease and Transplant TîrguMureş, including original patient records and echocardiographic data, was reviewed to identify patients diagnosed with HCM. All patients under 18 years of age diagnosed with HCM were included in the study. Patients

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were divided into two groups: group 1 included patients diagnosed before 1 year of age, and group 2 – patients diagnosed after 1 year of age.

Measurements

Medical records were reviewed to determine data regarding familial history of HCM or sudden cardiac death, personal history (age at time of diagnosis, symptoms, clinical findings, treatment), and echocardiographic parameters from the latest follow-up. The following echocardiographic parameters were noted: end-diastolic ventricular septal thickness reported to body surface area (as a Z score), left ventricular end-diastolic posterior wall thickness reported to body surface area (as a Z score), type of hypertrophy (asymmetric septal hypertrophy was defined as a septal to posterior left-ventricular free wall ratio of greater than 1.5 [22]), peak systolic gradient in the left ventricular outflow tract (LVOT), diastolic function of the left ventricle.Left ventricular outflow tract obstruction was defined as anatomic narrowing, together with a measured peak systolic gradient > 15 mmHg from echocardiography [23].

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 20, Chicago, IL, USA). Data were labelled as nominal or quantitative variables. Nominal variables were characterized by means of frequencies. Quantitative variables were tested for normality of distribution using Kolmogorov-Smirnov test and were described by mean ± standard deviation or median and percentiles (25; 75%), whenever appropriate. The frequencies of nominal variables were compared with a chi-square test. Differences in the mean or median between groups were analyzed using the t test, Mann–Whitney test, and Kruskall Wallis when appropriate. The level of statistical significance was set at $p<0.05$.

Results

A total of 39 patients with HCM were identified. Group 1 included 17 patients and group 2 included 22 patients. The median age at diagnosis was 0.4 years (IQR, 0.1 to 1 year) in group 1, versus 5 years (IQR, 1.1 to 17 years) in group 2 (p=0.0001).

In group 1, the sex distribution was almost equal (52.9% females versus 47.1% males), but in group 2 a higher incidence was found in boys than in girls (63.6% versus 36.4%).

Positive familial history of HCM, with at least one affected family member, was found in both groups, with a slight predominance in group 1 (6 cases –35.3% in group 1, versus 3 cases – 13.6% in group 2), but the difference was not statistically significant (p=0.11). All of these cases were registered in obstructive forms of HCM. It is important to be mentioned also that group 1 included two siblings, in whom there was at least one adult member known to be affected by this disease.

Concerning symptoms, syncope was found in four cases, all of them in group 1 (p=0.02; odds ratio 15; 95% CI, 0.7473 to 301.1) (Figure 1).

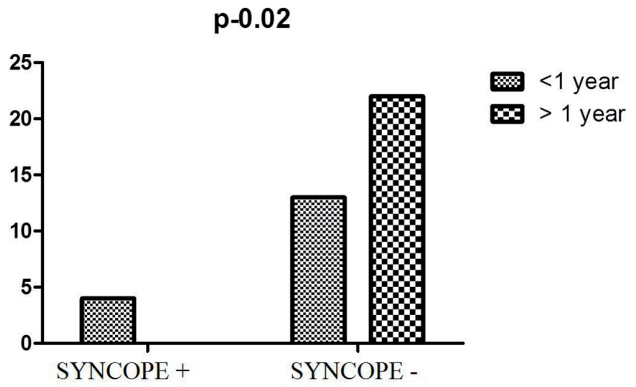

Fig. 1. Presence of syncope in the studied groups

Asymmetric septal hypertrophy was predominant in group 1 (64.7%), while in group 2 concentric left ventricular hypertrophy predominated (54.5%) (p=0.23). The median septal to posterior left-ventricular free wall ratio was 1.61 (IQR 0.92 to 3.9) in group 1 versus 1.425 (IQR 0.87 to 5.73) in group 2 (p=0.61).

The median Z score for septal end-diastolic ventricular septal thickness was 6.64 (IQR 2.43 to 28.56) in group 1 versus 11.75 (IQR 0.84 to 44.33) in group 2 (p=0.049) (Figure 2).

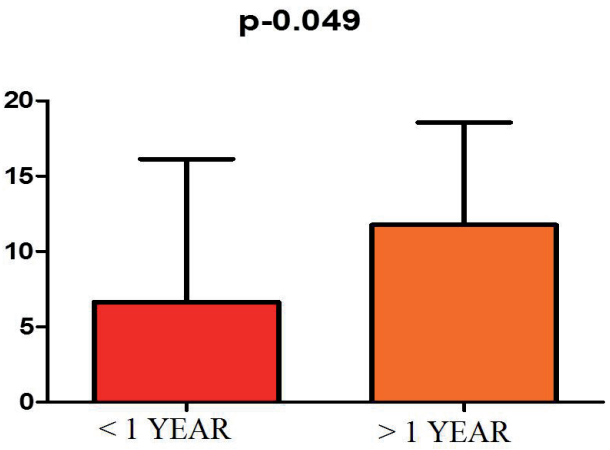

Fig. 2. The median Z score for septal end-diastolic ventricular septal thickness

The median Z score for left ventricular end-diastolic posterior wall thickness was 3 (IQR 0.46 to 13.18) in group 1 versus 3.415 (IQR -0.64 to 17.08) in group 2 (p=0.81).

Left ventricular outflow tract obstruction with a resting gradient was present in 14 cases in group 1 (82.4%) versus 13 cases (59.1%) in group 2 (p=0.11). The median peak instantaneous gradient was 89 mmHg (IQR 21 to 180 mmHg) in group 1, and 105 mmHg (IQR 18 to 198 mmHg) in group 2 (p=0.77).

Diastolic function of the left ventricle was impaired more predominantly in group 1 (p=0.0274; odds ratio 11.67; 95% CI, 1.526 to 89.17) (Figure 3).

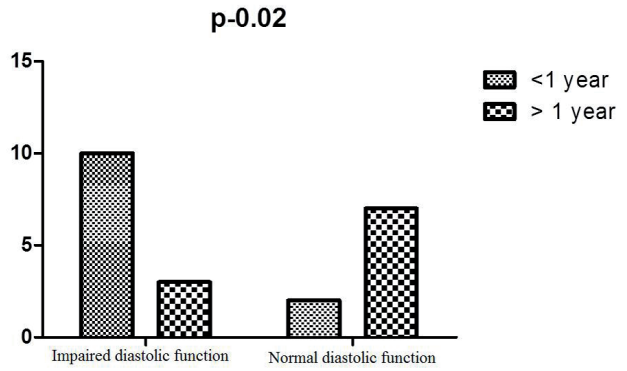

Fig. 3. Diastolic function of the left ventricle

Right ventricular hypertrophy was found in 4 cases in group 1, versus 1 case in group 2 (p=0.1474; odds ratio 6.462; 95% CI, 0.6488 to 64.35).

Four patients from group 1 and three patients from group 2 underwent septal myectomy to relieve left ventricular outflow tract obstruction. The median age at the time of the procedure was 5.4 years (IQR 5 to 7.7 years) in group 1, and 8 years (IQR 5 to 8 years). The overall median peak echocardiographic gradient before surgery was 109mmHg (IQR 57 to 160 mmHg),at first month follow-up the median gradient was 40 mmHg (IQR 8 to 65 mmHg) and at latest follow-up was 66 mmHg (IQR 18 to 147 mmHg) (p=0.008) (Figure 4).

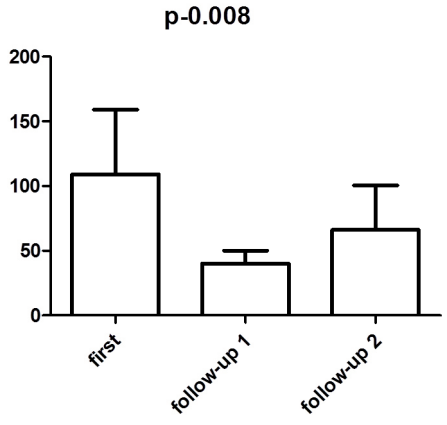

Fig. 4. Left ventricular outflow tract gradient before and after miectomy.

Discussions

As shown in our study, HCM can affect children of any age, demonstrating extensive clinical variability with regard to age of onset, severity and progression of disease.

Regarding the gender distribution, studies in specialized literature report the incidence of HCM to be 69% more common in males [5]. In our study, we found no significant difference between genders in patients diagnosed during infancy, but a higher incidence was found in males in group 2.

HCM often occurs in families, with an identifiable inheritance pattern, but many sporadic cases are also identified [7]. Some studies reportthe presence of familial disease in infants and children in less than 20% of cases [6, 23]. Recent data classify two-thirds of children as having idiopathic disease [8]. In our study we found a positive familial history of HCM in both groups, with a slight predominance in patients diagnosed during infancy (35.3% in group 1; 13.6% in group 2), but the difference was not statistically significant (p=0.11). In both groups, the remaining cases were considered to be idiopathic forms, a finding that is consistent with the results reported in international studies [8]. Group 1 also included two siblings affected by HCM; in their case, there was at least one adult member known to be affected by this disease who died suddenly (an uncle). Their parents were evaluated by echocardiography, but they didn't show any sign of left ventricular hypertrophy, demonstrating that genotype-phenotype relations vary greatly. In this case, a genetic test becomes mandatory in order to identify phenotype negative family members with subclinical manifestation of the disease. Genetic testing for mutations in the genes encoding cardiac sarcomere proteins isn't available yet in our center, mainly due to its high cost and lack of advanced methods in genetic testing.

One of the risk factors for sudden cardiac death in HCM is represented by the presence of syncopal episodes [24-26]. In our study, we found syncope in four cases, all of them in group 1, demonstrating a 15 times higher risk for syncope in children diagnosed in infancy compared to children diagnosed after 1 year of age. This is consistent with the international studies, that show a higher mortality for HCM presenting in infancy [20,21], one of the risk factors for poor outcomes being young age [19].

Although we found that asymmetric HCM predominated in group 1 (64.7%), while in group 2 concentric left ventricular hypertrophy was more frequent (54.5%), the difference was not statistically significant (p=0.23). Also, we found no significant difference concerning the presence and the severity of left ventricular outflow tract obstruction between the two study groups. Biventricular hypertrophy was found predominantly in group 1, but the difference was not statistically significant. These findings demonstrate once again the extensive variability of this disease.

In our study, both the median Z score for septal end-diastolic ventricular septal thickness and the median Z score for left ventricular end-diastolic posterior wall thickness were found more pronounced in group 2, demonstrating that the degree of hypertrophy has a progressive character throughout childhood.

The assessment of the diastolic function of the left ventricle showed an impairment more predominantly in group 1, demonstrating a 11.67 times higher risk for diastolic

dysfunction in children diagnosed in infancy compared to children diagnosed after 1 year of age.

In both adults and children with HCM, surgical relief of left ventricular outflow tract obstruction has been shown to be effective in reducing symptoms, with a significant reduction in the left ventricular outflow tract gradient [27-30]. In our study, there was also a significant reduction in the gradient, more pronounced at the initial evaluation after surgery compared to the latest follow-up, due to the fact that septal hypertrophy has the potential of reappearing.

Conclusion

Hypertrophic cardiomyopathy can affect children of any age, demonstrating extensive clinical variability with regard to age of onset, severity, progression of disease, and the risk of sudden death. Familial HCM was found having a slight predominance in patients diagnosed before 1 year of age. Patients diagnosed during infancy have a higher risk to develop syncope during childhood, confirming that the prognosis for infants with HCM is worse than in older children. A higher risk for diastolic dysfunction was also found in children diagnosed during infancy. The pattern of left ventricular hypertrophy showed a progressive character. Therefore, early diagnosis is highly important for improving management and prognosis of infants and children with HCM. Testing for mutations in the genes encoding cardiac sarcomere proteins should be available for identifying children with subclinical manifestation of the disease, especially in the familial context.

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