Diagnostic, Prognostic, and Therapeutic Implications and Outcomes of Children with Primary Hypertrophic Cardiomyopathy in Kosovo

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Abstract

BACKGROUND: Hypertrophic cardiomyopathy (HCM) is a primary disease of the myocardium in which a portion of the myocardium is hypertrophied (thickened) without any obvious cause, creating functional impairment of the cardiac muscle. It is a leading cause of sudden cardiac death in young athletes. The occurrence of HCM is a significant cause of sudden unexpected cardiac death in any age group and as a cause of disabling cardiac symptom.

AIM: The aim of the study was identification of the manifestations, assessment, and follow-up of children with HCM by transthoracic echocardiography as an important tool for clinical management and better understanding of the pathogenesis of HCM.

MATERIALS AND METHODS: We present a comprehensive analysis of 43 patients seen in Kosovo, with clinical and echocardiographic signs of HCM. Retrospectively, we analyzed medical records, treatment, and outcomes of those children, who have continued follow-up at our institution.

RESULTS: Twenty-three of them were male, aged between 4 months and 9 years at the first presentation (median of 2 years and 3 months). Cardiac failure, seen in almost half of them, was the most frequent presenting feature. At admission, the chest radiographs revealed an increased cardiothoracic ratio, to a mean of 72% in 5 infants and to 65% in 37 older children. Measured by transthoracic echocardiography, 28 patients had asymmetric hypertrophy of the left ventricle while 15 had concentric hypertrophy. The left ventricular ejection fraction was depressed in 21 patients. Patients with cardiac failure received various combinations of diuretics, B-blockers, angiotensin-converting enzyme inhibitors, and aspirin. Death occurred in 8 patients, in 4 of them shortly after admission; 4 patients left Kosovo and continued examination abroad, and the remaining 32 were followed up for a mean 42 months, with a range from 5 to 115 months. Surgical intervention was not performed on any of them despite the clinical and echocardiographic indications. Recovery was noted in 14 patients but requiring anti-failure medications. Slightly over two-fifths died. Of those with asymmetric form, 45% died, in half of those presenting in infancy, and 89% of those who presented at admission with signs of cardiac failure.

CONCLUSION: With the exception of the studies of pacing, no conclusive evaluations of treatments for HCM have been conducted. Management strategy is, therefore, based largely on clinical experience and consensus of many specialists.

Introduction

Hypertrophic cardiomyopathy (HCM) is typically defined by the presence of unexplained left ventricular hypertrophy (LVH). The clinical manifestations of HCM range from asymptomatic LVH to progressive heart failure to sudden cardiac death (SCD) and vary from individual to individual even within the same family. Common symptoms include shortness of breath (particularly with exertion), chest pain, palpitations, orthostasis, presyncope, and syncope.

HCM is defined as the presence of hypertrophied, non-dilated ventricle in the absence of a hemodynamic disturbance that is capable of producing the existent magnitude of wall thickening (e.g., hypertension, aortic valve stenosis, hypertrophy, catecholamine secreting tumors, etc.) [1]. It is the most common inherited cardiovascular disease, with diverse etiology, affecting population worldwide, and the leading cause of SCD in young people. Sarcomeric gene defect has been reported to be the primary cause of HCM in adults, but in children, the disease is seen in a wide variety of multisystem and cardiocirculatory disorders. It is common to group these diseases as familial, syndromic, neuromuscular, and metabolic (storage disease and mitochondrial disorders) [2].

HCM in childhood is a heterogeneous disease with variable presentation and has been reported and described from several centers and countries.
Incidentally, most of the reports have drawn attention to the generally severe course of the disease, especially to its unsatisfactory response to standard anti-failure therapy. Reports have mostly come from tertiary centers, raising the possibility of a selection bias in favor of very sick children [3]. Unfortunately, till now, reports from Balkans countries of the disease are scanty.

The aim of this article was to present a diagnostic approach, treatment, and outcomes of children with HCM in Kosovo, as a small country with limited technical and human resources to compare with recent publication in this field.

Materials and Methods

The primary objective of this study was to provide an account of children (aged from 4 months to 9 years) with HCM as seen in the country of Kosovo, diagnosed by echocardiography, analyzing the data of 43 patients, registered at the Unit of Cardiology, from January 2007 to December 2017.

Pediatric Clinic in Pristina, part of the University Clinical Center of Kosovo in Pristina, Kosovo, provides pediatric cardiology services of secondary and tertiary level. Practically, all children with known or suspected cardiac disease are referred to us from the regional hospitals for cardiac evaluation and care. This system has enabled us to provide for virtually all patients with pediatric cardiac disease in Kosovo and to build a database. This study is part of data relating to HCM that forms the material for this study, which aimed to provide an account of the disease as seen in Kosovo. The study protocol was approved by the medical ethics committee of the University Clinical Center of Kosovo in Pristina (date July 26, 2018, N 1098). Written informed consent was obtained from all patients and guardians.

We commenced our study in January 2007 and recorded summaries of patients with cardiac disease in the cardiology department database. A single pediatric cardiologist in the department of cardiology evaluated cardiological examination, where 43 children, aged between 4 months and 9 years at the first presentation, fulfilled the standard criteria for the diagnosis of HCM, and they formed the subjects of this study. From the study have been excluded all children with left ventricular hypertrophy and known etiology – children with arterial hypertension, mucopolysaccharidosis. The evaluation of each child comprised a short familiar and personal history, physical examination, chest radiograph, electrocardiogram, and echocardiography. Determination of levels of the cardiac enzymes in serum was not considered a critical investigation.

Weight and stature were recorded and the body surface area was calculated by the Dubois and Dubois formula. None of the patients was receiving cardiovascular medication at the time of admission. In all patients, the echocardiographic studies at presentation and during follow-up were performed by the same two pediatric cardiologists. Follow-up investigations, comprising mostly of chest electrocardiograms and echocardiographs, were performed as often as the clinical state warranted. The results obtained are shown in absolute and relative numbers.

Results

Both sexes were affected, there being 23 males (53%) and 20 females. At initial presentation, all patients have been aged between 3 weeks and 9 years, the median age being 13 months and mean 22.33 months. Of this number, 8 (18%) were less than 12 months; 23 (53%) were aged between 1 and 5 years, and 12 (28%) were more than 5 years of age. For half of them, the reason for cardiac examination was a systolic heart murmur. At admission, the chest X-ray revealed an increased cardiothoracic ratio, to a mean of 72% in 5 infants and to 65% in 37 older children. All of the patients were Kosovar Albanians and citizens of Kosovo.

Etiology

In 18 (41%) patients, siblings had reportedly suffered from the same disease, and these patients were categorized as being familial. Four of them (three males and one female) were cousins, 16 members of this family were suffering from HCM. Of the number in this family, 7 died during study period (one child and six adults), and all had sudden death. In 4 patients (9%), there was LEOPARD syndrome, but without pulmonary hypertension. In the remaining patients, etiology of HCM was unknown.

Clinical state at presentation

At presentation, we found evidence of congestive heart failure in 4 children, in other 12, an atypical heart murmur was noted during the routine examination, while the remaining 27 were referred for cardiac examination following radiographic examination and disturbances in cardiothoracic ratio. The cardiothoracic ratio in this group of patients ranged from 44% to 76% with a mean of 58%. In other 26, in whom the ratios could accurately be evaluated, they ranged from 59 to 77, with a mean of 65%.

Medication

All four patients who presented with congestive heart failure received various combinations of standard
anti-failure drugs. Later in the course of the disease, three patients received infusions of amiodarone when they developed ventricular rhythm disturbances and became critically ill. Furosemide and spironolactone were standard part of the therapy during the whole time of hospitalization. Of the 28 patients, including 4 with signs of cardiac failure, received captopril and 8 of them developed a captopril-induced intolerable cough, which necessitated the drug replacement by enalapril. All patients initially were treated with propranolol but carvedilol was additionally administrated in four patients, because intolerable hypotension was developed. In 28 patients, we instituted empirical treatment with aspirin.

Follow-up and outcome

Of our overall group, four patients died shortly after admission (4–7 days) and four died at home with signs of arrhythmia or sudden death, despite therapy coverage. Five of them with positive anamnesis data of familiar form of cardiomyopathy were taken away.

Management of symptoms

HCM is an important disease affecting populations worldwide. The primary purpose of screening for HCM is to identify affected children before the experience sudden death. Early recognitions of the disease, either in the pre-clinical stage (before LVH develops) or in the clinical stage (after LVH has developed), may allow for earlier treatment with the potential to alter disease progression. A secondary aim of screening would be to identify family members with either pre-clinical or clinical disease, thus offering them the same therapeutic benefits as offered to the index case. As a result of these phenotypic and age-related variations, any diagnostic or screening strategy for HCM must include a variety of components. These range from simple measures such as personal and family history, the physical examination, electrocardiography, or echocardiography as we presented in Table 1 [4], [5].

Discussion

HCM is a complex disease with variation in presentation, symptoms, severity, and response to therapy and the goals of the therapy in HCM are symptom control and prolongation of survival. The clinical importance of outflow obstruction to the natural history of HCM and the associated symptoms has been highly controversial. The presence of outflow tract obstruction has not been found to be associated with an increased risk of sudden death; patients with outflow tract obstruction are at greater risk for symptoms and progression to death due to heart failure. Although the ability to define the etiology of HCM has improved overtime, this goal still remains elusive [6], [7]. Even in our study, we have not found any association between outflow obstruction and mortality rate.

Contrary to recent progress in treatment, children with HCM therapy based on the use of beta-blockers, calcium channel blockers, antiarrhythmic drugs (disopyramide and amiodarone), pacemaker therapy (asynchronous ventricular pacing), implantation of the intracardiac defibrillator, and in extremely severe forms surgical myectomy and percutaneous radiofrequency septal reduction [8], [9]. Our account of HCM based on experience in a national referral center in Pristina corroborates the dismal accounts of the disease which have been published previously from other centers. During a mean follow-up of 46 months, approximately one-sixths of the patients died, other improved but continued to require anti-failure and anti-arrhythmic medications. Furthermore, these figures raise the very important question on why the standard medical treatment of the disease is so frequently unsatisfactory (Table 2).

Table 2: Summary of the some publications on childhood hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Year</th>
<th>Country</th>
<th>Etiology</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maron [1]</td>
<td>2000</td>
<td>USA, Italy</td>
<td>Mixed</td>
<td>744</td>
</tr>
<tr>
<td>Sandoval [17]</td>
<td>2006</td>
<td>Germany, USA</td>
<td>Mixed</td>
<td>320</td>
</tr>
<tr>
<td>Veselka [18]</td>
<td>2014</td>
<td>Europe</td>
<td>Mixed</td>
<td>117</td>
</tr>
<tr>
<td>Williams [19]</td>
<td>2015</td>
<td>USA</td>
<td>Mixed</td>
<td>50+50</td>
</tr>
<tr>
<td>Jose Oliva-Sandoval [20]</td>
<td>2010</td>
<td>Spain</td>
<td>Mixed</td>
<td>152</td>
</tr>
</tbody>
</table>

While many children with HCM are asymptomatic, some typical prognostic profiles are well recognized. One group of patients has symptoms of cardiac failure, including exertional dyspnea, orthopnea, chest pain, and general fatigue. This group of patients has normal or hypercontractile left ventricular function,
with or without obstruction of the left ventricular outflow tract (LVOT). While significant obstruction typically causes symptoms, there are also asymptomatic patients who do not have obstructed outflow tract, and symptoms are due to factors such as diastolic dysfunction, mitral regurgitation, or microvascular dysfunction [10], [11]. Most children in our study with clinical manifestation of HCM belong to the first group (19 children), no child is registered in the second group, and 7 children were registered in the third group, all having family CMP (Table 3).

Hypertrophic obstructive cardiomyopathy is an uncommon cause of LVOT obstruction in children. In symptomatic patients, open heart surgical myectomy has hitherto been the only therapeutic option. Recent data in treating patients with obstructive form of the HCM using percutaneous radiofrequency septal reduction, as an alternative to surgical myectomy, from many centers showed enviable results, especially after having failed pharmacological therapy [12], [13]. Transthoracic and transesophageal Doppler echocardiography is a gold standard to document the degree of myocardial septal hypertrophy and the resting gradient across the LVOT. Twelve children from our study group developed severe form of obstructive cardiomyopathy, and based on the technical limitation, none of the children was not treated surgically or using radiofrequency procedure Figure 1 [14], [15].

At present, cardiac transplantation is the ultimate surgical resort for patients who do not respond to medical or surgical treatment. However, the option is available only in relatively few centers, most of them in the United States of America and in Europe (Table 2) [2], [3], [16], [17], [18], [19]. For the pediatric cardiologist who has no recourse to cardiac transplantation, caring for child with HCM and treatment-resistant cardiac failure remains a very challenging assignment [20]. Quite often, the choice must be made between continuing treatment with barely effective conventional drugs, adding carvedilol and amiodarone despite their ill-defined pediatric dosing and lingering uncertainties about efficacy in children. In all probability, the choice will be influenced as much by the available resources as by the embraced philosophies of care [21], [22].

### Study limitations

A limitation of our study relates to the diagnosis of pathohistological type of HCM which, for the technical reason, was completely based on the clinical examination. Indeed, the recent statement of the American Heart Association on cardiomyopathies does not recommend the test for the diagnosis of disease. Endomyocardial biopsy, evaluated using the Dallas criterions, remains the gold standard for the diagnosis. But even that test is not fail-proof. Endomyocardial biopsy is not feasible in most centers that provide care for children with cardiac disease [22]. The clinical implication of all these factors is that in many centers, including ours, the etiology of HCM is often uncertain. In the absence of etiology, treatment aimed at the cause is either impossible or, at best, empirical. A limitation of our study with regard to the treatment was also inability to prevent the sudden death, based on the implantation of the intracardiac defibrillator. Despite the strong indication for this treatment and sudden death of four members from of the same family, none of the children from our study group was treated with the defibrillator.

### Conclusion

HCM in our patients mostly have been presented in severe form, causing nearly one-sixth death during the study period. While the clinical diagnosis is usually easy, and the hemodynamic severity can be ascertained fairly accurately, the etiology is frequently uncertain. The response to standard anti-failure medical and surgical treatment is often unsatisfactory and cardiac transplantation is not feasible. For now, hopes of improved survival in our, and similar centers, are hinged on on-going international efforts to manipulate multifactor mechanisms implicated in HCM.

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**Table 3: Age at diagnosis, standard, and antiarrhythmic drugs and age at death of children with hypertrophic cardiomyopathy at our study**

<table>
<thead>
<tr>
<th>Initials of children</th>
<th>Age at diagnosis</th>
<th>Standard medical therapy</th>
<th>Antiarrhythmic therapy</th>
<th>Age at death</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.L. (male)</td>
<td>19 months</td>
<td>Captopril, furosemide</td>
<td>Sotalol (start) +</td>
<td>32 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&amp; aspirin spironolactone</td>
<td>amiodarone (continue)</td>
<td></td>
</tr>
<tr>
<td>B. A (female)</td>
<td>11 months</td>
<td>Enalapril, furosemide</td>
<td>Sotalol (start)</td>
<td>26 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&amp; aspirin spironolactone</td>
<td>&amp; felodipine (continue)</td>
<td></td>
</tr>
<tr>
<td>A.S. male</td>
<td>8 months</td>
<td>Captopril, furosemide</td>
<td>Atenolol (start) +</td>
<td>3 years 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&amp; aspirin spironolactone</td>
<td>amiodarone</td>
<td>months</td>
</tr>
<tr>
<td>S.D. male</td>
<td>33 months</td>
<td>Enalapril, furosemide</td>
<td>Sotalol (start) +</td>
<td>6 years 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&amp; aspirin spironolactone</td>
<td>amiodarone</td>
<td>months</td>
</tr>
</tbody>
</table>

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**Figure 1**: Parasternal left ventricular long-axis echocardiographic section in diastole (a) and systole (b) in a patient with hypertrophic cardiomyopathy. LV - left ventricle, LA - left atrium, Ao - aorta, MV - mitral valve
References


