Progress in Pediatric Cardiology 31 (2011) 13–19

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Review

Treatment of hypertrophic cardiomyopathy in childhood ☆

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ARTICLE INFO

Keywords:
Cardiomyopathy
Hypertrophic cardiomyopathy
Sudden death
Pediatrics
Children
Infants

ABSTRACT

Hypertrophic cardiomyopathy (HCM) in children is a rare disorder characterized by marked diversity both in terms of etiology and outcome. These factors combine to limit the body of data available concerning the impact of therapy on outcome, particularly when considered in a cause-specific fashion. Because of the limited pediatric data, guidelines for management of HCM in adults have been broadly adapted for use in pediatrics. The relevance of these recommendations to the pediatric HCM population remains uncertain but it is clear that there are situations in which considerations unique to the pediatric population need to be taken into consideration. This review describes the general approach to evaluation and treatment with specific discussion of those situations in which pediatric-specific considerations are important, including genetic evaluation, medical and surgical management of symptoms, and interventions intended to prevent sudden death.

Hypertrophic cardiomyopathy (HCM) is defined as the presence of a 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, catecholamine secreting tumors, hyperthyroidism, etc.) [1]. Sarcomeric gene defects have 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 cardiospecific disorders. It is common to group these diseases as familial, syndromic, neuromuscular, and metabolic (storage disease and mitochondrial disorders) [2]. It is worth noting that the nomenclature is controversial, with some observers recommending that the term "hypertrophic cardiomyopathy" be reserved for disease due to sarcomeric gene defects [3]. The recommendation of this publication was that other causes, for example, Noonan syndrome, would be called "left ventricular hypertrophy associated with Noonan syndrome". There are a number of reasons why this approach has not been accepted within pediatric cardiology. This same publication defined HCM phenotypically as "hypertrophied, non-dilated LV in the absence of another systemic or cardiac disease that is capable of producing the magnitude of wall thickening evident (e.g., systemic hypertension, aortic valve stenosis)" [3]. This phenotypic definition has been in common use for many years, as recognized by the 1995 World Health Organization International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies [4]. Virtually all prior publications in pediatrics have used this definition, and efforts to change terminology that is in common use are notoriously unsuccessful because language usage evolves primarily by consensus usage, not in response to the preferences of specific individuals or committees, particularly when the terminology is etymologically accurate. The term "hypertrophic cardiomyopathy" describes the phenotype, and typically the evolution of medical terminology has been characterized by adding the etiologic to the phenotypic terminology when it is known. For example, pneumonia describes a disease state that can have subcategories of viral pneumonia, bacterial pneumonia, fungal pneumonia, etc., based on the commonality of the phenotype despite the fact that these forms have different etiology, therapies, and outcomes. A similar approach is in common use for HCM, for example, the terms "sarcomeric HCM" and "Noonan HCM" adequately distinguish these two etiologies and communicate both the etiology and phenotype. In contrast, terms such as "Noonan syndrome with left ventricular hypertrophy" do not communicate the fact that this is a form of cardiomyopathy rather than simply a single clinical finding that could be due to other causes in these patients, including hypertension. Noonan HCM is phenotypically identical to sarcomeric HCM, that is, absence of a hemodynamic cause, myocardial disarray, regional variation in hypertrophy, frequent presence of dynamic left ventricular outflow tract obstruction, regional myocardial fibrosis, a risk for congestive heart failure and death due to diastolic dysfunction, and a risk for arrhythmic sudden death. This phenotype is intrinsic to the term HCM, in contrast to the term "left ventricular hypertrophy". If the recommendation that the term "left ventricular hypertrophy"

☆ This work was supported by grant 5 R01 HL53392-09 from National Institutes of Health.
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doi:10.1016/j.ppedcard.2010.11.004

were to be used in patients without a sarcomeric gene mutation, the overwhelming number of patients with the HCM phenotype would have to be called "idiopathic left ventricular hypertrophy" because they have not had a sarcomeric gene defect identified, either because they have not undergone genotyping or else they fall into the 40–50% of individuals for whom a sarcomeric defect cannot be identified despite genotyping. Therefore, in this review, HCM will be used to refer to the phenotype with etiologic modifiers added when relevant.

Most of the available information for treatment of HCM derives from studies in adult populations, and the implication of these observations for pediatric populations is often uncertain. This review will summarize the relevant data in adults and to discuss their implications for the management of children with HCM.

1. Epidemiology and Survival

The Pediatric Cardiomyopathy Registry (PCMR) is a multicenter observational study of pediatric cardiomyopathies initiated in 1995. A 2007 report from the PCMR described the distribution of etiologies and the etiology-specific survival in 849 children [5]. Overall, there was nearly equal distribution between inborn errors of metabolism (IEM, 9%), malformation syndromes (MFS, 9%), and neuromuscular disorders (NMD, 8%), with the remaining 75% represented by the idiopathic and familial HCM (FHCM) patients. The mean age at diagnosis was under 6 months in the IEM and MFS groups whereas the other groups were typically older at the time of diagnosis. Survival was found to be etiology- and age-specific, confirming earlier observations that survival in infants is much poorer than in other age groups, attributable in large part to the high incidence of IEM and MFS in infants. In contrast, survival for patients with NMD and FHCM was similar regardless of age at diagnosis. A notable observation was that annual mortality in children who did not have IEM or MFS was about 1% per year, which compares favorably with contemporary reports in adults with familial HCM. This finding contrasted to earlier and smaller series in children that reported much higher annual mortality.

2. Etiology-Specific Therapy for HCM

Although the ability to define the etiology of HCM has improved over time, this goal still remains elusive. The infant with HCM in particular represent a particularly difficult challenge in this regard due to the wide range of disorders for which an association has been reported [1]. At present, etiology-specific therapy is available only for a few disorders, predominantly for inborn errors of metabolism such as Pompe disease and other lysosomal storage disorders [6]. However, establishing cost-effective methods for the determination of specific etiology is an important step in the process of developing and testing etiology-specific therapies, and in this regard important progress has been made. Nevertheless, although the pace of advances in genetic and metabolic diagnostics has quickened and the chances that a specific diagnosis can be achieved has improved substantially in recent years, about 50% of HCM cases under age 1 remain idiopathic [5]. Amongst those patients for whom a defined etiology is identified, a few disorders (Pompe disease, Noonan syndrome and related disorders such as Costello and LEOPARD Syndrome, and sarcomeric mutations) account for the largest percent and etiologic diagnosis in the remainder remains far more difficult. From the cardiac perspective, the association of particular patterns of the cardiac phenotype with specific etiologies has been an area of considerable interest because of the potential to guide the evaluation. For example, the finding of a hypertrophic, hypokinetic left ventricle has been most frequently associated with IEM, and in particular with mitochondrial defects. Biventricular outflow tract obstruction is more common in Noonan syndrome than in other forms of infantile HCM. Asymmetric patterns of hypertrophy are more commonly seen in syndromic and familial HCM than in IEM. Although these sorts of observations can provide some guidance, for most infants with HCM early referral for multi-specialty evaluation including specialists in cardiology, neurology, genetics, and metabolism is warranted. The management of the inborn errors of metabolism is driven largely by the underlying genetic defect, whereas this review will focus primarily on the management of sarcomeric defects in children.

3. Genetics and Genetic Testing

The genetic transmission of FHCM is usually autosomal dominant, although maternally inherited pattern of transmission has been reported. The accumulation of new genetic information since the early 1990's has led to the observation that a large number of mutations in multiple proteins manifest clinically as HCM. The results of molecular studies so far have implicated a number of sarcomeric and sarcomere-associated proteins in the etiology, including beta-myosin heavy chain, alpha-myosin heavy chain, myosin essential light chain, myosin regulatory light chain, cardiac troponin T, cardiac troponin I, alpha-tropomyosin, and myosin binding protein C, titin, and actin [7]. These gene mutations are characterized by allelic heterogeneity; that is, multiple distinct mutations of each of these genes can cause the disease. The frequent finding of mutations in the sarcomeric proteins resulted in the paradigm of FHCM as a disease of the sarcomere [8], but it is now clear that a similar phenotype can be seen with mutations in genes encoding non-sarcomeric proteins within the *z*-disc and calcium handling control mechanisms as well as the Ras/MAPK pathway syndromes (Noonan Syndrome, Costello Syndrome, Cardiofacialcutaneous syndrome, and LEOPARD syndrome) [7,9]. There are also familial forms of HCM due to non-sarcomeric genes, such as those due to mitochondrial defects, potassium channel [10], and the gamma subunit of protein kinase A [11]. Although sarcomeric defects appear to be the most common cause of FHCM, they are not the only cause. With the availability of commercial genetic testing for most of the identified sarcomeric genes, it has become clear that the genotype responsible for the HCM phenotype cannot be determined in 30–40% of patients, indicating that there may be a substantial number of additional non-sarcomeric genes that contribute to this disorder.

The availability of commercial genetic testing has also prompted considerable debate concerning who should have this testing performed. The initial expectation that identification of the responsible mutation would markedly improve risk stratification and clinical management has not materialized [12]. For example, early reports indicated that mutations in troponin T have a consistent phenotype of mild or absent hypertrophy associated with a high incidence of sudden death [13], but families have now been described with troponin T defects who have a low risk of early death [14]. Other factors, such as the coexistence of mitochondrial DNA mutations in some families [15], multiple mutations [16], or the impact of coexistent genetic polymorphisms within the renin–angiotensin system [17] account for some of the variability in disease expression. Because of the lack of impact of genetic testing on clinical management, many observers do not feel there are sufficient benefits associated with genotyping to justify the cost and the potential for adverse psychological and social consequences [18].

A stronger case can be made for genotyping in infants, children, and young adults. Because development of the phenotype can be noted throughout childhood, current practice is to periodically screen all offspring of affected individuals throughout childhood despite the fact that 50% of these children do not carry the gene. Children who are found to carry a familial gene can be followed more closely for development of disease and become eligible for trials of interventions to prevent development of the phenotype. Children who are genotype negative do not require longitudinal evaluation, markedly reducing