Management of pediatric hypertrophic cardiomyopathy

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Purpose of review

As the underlying genetic basis of hypertrophic cardiomyopathy is being characterized, there has been increasing recognition of the wide spectrum and variable evolution of this disease within the pediatric age range. This review outlines recent evidence relevant to the diagnosis, management, and prognosis of hypertrophic cardiomyopathy specific to children and adolescents.

Recent findings

Studies of putative causal genes are leading to the discovery of factors affecting the variability of phenotypic expression and possible avenues for new therapies. Nonetheless, the use of genetic testing currently remains for research purposes only. Echocardiography is the primary means for evaluation, with an increasing focus on diastolic performance. Useful prognostic information can be obtained from the safe performance of cardiopulmonary stress testing. Sudden death can occur in children, although the risk factors are likely different than in adults. The role and mechanisms for possible ischemia remain controversial, and likely differ between individuals. Activity restrictions are recommended, with medical therapy reserved for those who are symptomatic. For those with important left ventricular outflow obstruction, surgical myectomy may be indicated, with little current role for alcohol septal ablation. Advances in implantable defibrillators now make this therapy feasible in younger children.

Summary

There are important differences from adults in the approach to the diagnosis and management of hypertrophic cardiomyopathy in children and adolescents. Care regarding prognostication and therapy must be taken given the potential life-long implications.

Keywords

hypertrophic cardiomyopathy, prognosis, sudden death

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Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disorder marked by primary myocardial hypertrophy without an identifiable cause. While previously thought to be a rare disorder, HCM is now thought to occur with an incidence of 1 in 500 in the general population and remains the most common cause of sudden death in children and young adults less than age 35 years [1]. Early literature, limited to patients from a few tertiary care centers, had documented an annual mortality rate of 6% in children and adolescents with HCM. More recent data from a larger cohort of patients suggests a less malignant disease course with an annual overall mortality rate of 1% [2•]. Despite important medical advances in the past several years, HCM in children remains a diagnostic and therapeutic challenge for the cardiologist.

Diagnosis

Genetic evaluation

Since the first description of the genetic basis of HCM in 1989, major advances in genetic testing have occurred such that the genetically heterogeneous basis of HCM is well documented, with identification of at least 10 causative genes and over 150 identified mutations [3•]. Most of these mutations have been shown to be missense mutations with a single amino acid substitution within or close to important functional domains [4]. The involved genes encode sarcomere proteins, and thus affect the major contractile unit of the myocardium. Three genetic defects account for most cases of HCM, and include the beta MHC, myosin-binding protein C, and troponin T genes. While greater than 90% of patients with a beta MHC gene defect will demonstrate left ventricular hypertrophy in childhood, HCM secondary to mutations in one of the other genes may remain quiescent until adulthood [3•].

While earlier work identified the 10 causal genes, recent investigation has been directed toward identifying clinical correlates of specific intragenic mutations. The Toronto group recently identified nonconservative missense mutations within the beta MHC gene that are associated with an important decrease in survival when compared with conservative mutations involving the same gene [5•].

Unfortunately, genetic testing remains expensive, is confined to only a few research laboratories and, thus, is not universally available to most cardiologists treating children. In addition, published data from several centers indicate that mutations in sarcomeric protein genes account for only 60% of HCM cases [4]. Even for those with

an identified genetic mutation, there exists variable interfamilial and intrafamilial clinical expression for individuals with identical mutations [6]. Phenotypic expression of HCM is thought to be the production not only of the causal mutation, but also of modifier genes and environmental factors [7••]. Investigation of such gene modifiers is a current subject of considerable research. Aldosterone, through novel signaling proteins, has been identified as a major link between sarcomeric mutations and cardiac phenotype [8•]. Spironolactone has been shown to attenuate myocyte disarray in transgenic mouse models of human HCM [8•]. The potential beneficial effects of mineralocorticoid blockade in human HCM have not yet been studied.

Prenatal molecular diagnosis of HCM has recently been shown to be feasible [9], but given the genetic and clinical variability, may not become routine.

Clinical evaluation

Echocardiography

Two-dimensional echocardiography remains the primary diagnostic modality for identifying children with HCM. While previous recommendations involved intermittent echocardiographic assessments before age 18 years in those with a positive family history of HCM, it is now recognized that late onset may occur. Current recommendations for first degree relatives of affected family members include annual echocardiographic assessment in children ages 12 to 18 years and ongoing evaluation thereafter at intervals of every 5 years [7••]. Evaluation of children younger than age 12 years should be dictated by family history and clinical assessment. Affected children and young adults are to be observed at least annually.

In addition to the echocardiographic evaluation of chamber dimensions and the assessment of resting and provocable left ventricular outflow tract obstruction, assessment of diastolic performance is important. Diastolic abnormalities have been shown to be frequent in children with HCM, and due to the abnormalities in both the active component of the dissociation of actin and myosin in the early filling phase and the passive properties of the ventricle that affect compliance [4]. Diastolic dysfunction has been shown to be the primary cause of exercise intolerance in these patients [7••,10•]. The standard echocardiographic measures of diastolic performance have been found to have limited applicability in children with HCM, as they are largely dependent on loading conditions [10•]. In contrast, tissue Doppler imaging has proven to be a useful diagnostic tool for evaluating these patients. Tissue Doppler derived early transmitral left ventricular filling velocity (E/septalEa) ratio has been shown to predict adverse clinical outcomes including death, cardiac arrest, ventricular tachycardia, and important cardiac symptoms in children with HCM [10•].

Electrocardiography

Electrocardiographic assessment may be of diagnostic assistance in identifying preclinical carriers of HCM. Konno *et al.* [11] demonstrated that among 148 patients with an identified HCM genotype, the presence of Q waves of >3 millimeters in depth and/or >0.04 seconds in duration in at least two leads other than aVR was both sensitive and specific in identifying patients who would have a positive diagnosis on genotyping.

Ambulatory electrocardiographic Holter monitoring

Current clinical evaluation should include annual 24- or 48-hour Holter monitoring for assessing both atrial and ventricular arrhythmias. Holter monitor results aid in choosing a treatment regimen for the patient, as the presence of both nonsustained and sustained ventricular tachycardia are useful in stratifying risk of sudden death in young patients with HCM [12•].

Cardiopulmonary stress testing

Exercise testing remains an important part of the cardiologist's diagnostic armamentarium for assessing children and young adults with HCM. The safety of exercise testing in this group of patients has been recently confirmed in a large patient series [13•]. Peak oxygen consumption has been shown to correlate with both the presence of patient symptoms and impaired diastolic function [10•]. An impaired rise in systolic blood pressure with exercise continues to identify those young patients at increased risk for sudden cardiac death [3•,7••].

Magnetic resonance imaging

Evaluation with magnetic resonance imaging (MRI) is becoming increasingly more common in the evaluation of the pediatric patient with HCM [2•,14]. The extent of delayed hyper-enhancement of the myocardium may reflect the severity of myocardial damage [14].

Risk stratification

The primary goal in the treatment of children and adolescents with HCM is alleviation of patient symptoms and the prevention of sudden death. Risk stratification plays an important role in directing patient treatment. The highest risk for sudden cardiac death has been associated with the presence of any of the following: previous cardiac arrest or spontaneously occurring sustained ventricular tachycardia [7••], family history of a premature HCM-related cardiac death, particularly if sudden, in a close relative or multiple relatives [7••], identification of a high-risk mutant gene [7••], abnormal blood pressure response to exercise [7••], and nonsustained ventricular tachycardia noted on Holter monitor recording [7••,12•]. The role of extreme ventricular hypertrophy (interventricular septal thickness >30 millimeters) as a risk factor for sudden death remains controversial [7••]. There has been continued debate regarding the role of myocardial ischemia as

a potential cause of sudden cardiac death. While it is generally agreed upon that children and adolescents with HCM have the substrate for ischemia, the etiologies for the ischemia may be multiple. While myocardial bridging of an epicardial coronary artery branch (commonly the left anterior descending) has not been shown to be a predictor of sudden cardiac death in adults with HCM [15], surgical division of myocardial bridges in children with HCM has been shown to alleviate clinical findings of ischemia [16•], thus supporting the role of myocardial bridging as a factor for sudden cardiac death. Recent evaluation of coronary artery blood flow in response to infusion of the coronary artery vasodilator dipyridamole in adults with HCM has demonstrated the presence of coronary microvascular dysfunction [17]. The degree of microvascular dysfunction has been identified as a strong independent predictor of clinical deterioration and death.

Management

Activity restrictions

Physical activity restrictions remain of paramount importance for children and adolescents with HCM. An increase in catecholamine levels may precipitate both an increase in left ventricular outflow tract obstruction and myocardial ischemia. The latest American Heart Association statement on exercise guidelines for children with genetic cardiovascular diseases continues to advise that young patients with HCM refrain from competitive athletics and isometric activities [18•].

Medical

Medical management is reserved for those patients who are symptomatic. It remains controversial as to whether asymptomatic children with marked resting left ventricular outflow tract obstruction (systolic pressure gradients >75 mm Hg) should also be treated, with a view to halting further disease progression. Medical therapies, other than amiodarone, have not been documented to affect the risk of sudden death [7••]. Beta blockers continue to be at the frontline of medical therapies for children with HCM. They are useful for provocable left ventricular outflow tract obstruction occurring with exercise, but have not been documented to have any role in the amelioration of resting left ventricular outflow tract obstruction. Disopyramide, either alone or in combination with a β-blocker, has been shown to be useful in amelioration of resting or provocable left ventricular outflow tract obstruction or associated symptoms. Verapamil is best reserved for patients who do not have significant symptoms in the presence of left ventricular outflow tract obstruction as death has been reported to occur in this population receiving a calcium channel blocker.

Surgical

Surgical myectomy continues to be the standard of therapy for children with important symptoms in the presence of left ventricular outflow tract obstruction who are refractory to medical therapy. In experienced centers, the operative mortality is low and the procedure provides long-term relief of obstruction [7••]. Isolated surgical myectomy will not benefit those children with associated abnormalities of the mitral subvalvular apparatus, which can also be a source of obstruction. In these patients, resection of anomalous chordae or surgical relief of papillary muscle fusion in association with an extended septal myectomy has been reported to provide good surgical results and avoid the need for mitral valve replacement [19•].

Pacemaker/implantable cardiac defibrillator therapy

Randomized clinical trials that have been performed regarding pacing therapy have not shown an important benefit. There has been no new recent data to contradict these findings [1].

While HCM has been considered a clinical implication for implantable cardiac defibrillator placement in children [20••], careful patient selection is advised [7••,21•]. Because of the high frequency of complications, including death at implantation [21•], this therapy should be considered for patients for secondary prevention after an episode of resuscitated sudden death or for primary prevention for those patients with multiple risk factors [7••]. Newer implantable cardiac defibrillator modifications, including placement of a subcutaneous array in those children too small for consideration of a transvenous system [22•], makes this therapy in the young child more feasible.

Percutaneous alcohol septal ablation

This procedure involves the introduction of absolute alcohol into a target septal perforator branch of the left anterior descending coronary artery for the purpose of producing a myocardial infarction within the proximal ventricular septum. Septal hypokinesis and more remote remodeling occur, thereby relieving left ventricular outflow tract obstruction. While the procedure has been successful in providing intermediate-term resolution of outflow tract obstruction and associated symptoms in adults with HCM, the risks are not minimal and include heart block [23], ventricular septal rupture [24], and death [23]. The procedure has yet to be subjected to the scrutiny of randomized controlled studies or long-term follow-up [7••]. One of the major concerns regarding alcohol septal ablation relevant to the child or young adult with symptomatic obstructive HCM is the potential long-term risk for arrhythmia-related cardiac events, including sudden cardiac death, arising from the procedure itself. The risk of such an event may well outweigh the risk of sudden cardiac death from the disease itself and, for this and other reasons, there is no role for alcohol ablation in the treatment of children and adolescents [7••].

Conclusion

The diagnosis of HCM in children and adolescents is important, as there is a risk of both symptoms and sudden death. However, earlier diagnosis also leads to earlier onset of surveillance and management, which for these children must continue over the lifetime. The potential impact on long-term quality of life is great. Advances in the precision and utility of noninvasive assessment are important, as well as the development and evaluation of safe and effective therapies aimed at slowing the progression of the disease process, alleviating symptoms and lowering the risk of sudden life-threatening events.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Nishimura RA, Holmes DR. Hypertrophic obstructive cardiomyopathy. N Engl J Med 2004; 350:1320–1327.

2 • Frenneux MP. Assessing the risk of sudden cardiac death in a patient with hypertrophic cardiomyopathy. Heart 2004; 90:570–575.
This article outlines the potential mechanisms of sudden death in HCM and provides a review of both clinically useful established risk factors as well as clinical markers of unproven clinical utility.

3 • Chung MW, Tsoutsman T, Semsarian C. Hypertrophic cardiomyopathy: from gene defect to clinical disease. Cell Res 2003; 13:9–20.
This report provides a comprehensive outline of the molecular pathogenesis of HCM.

4 Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet 2004; 363: 1881–1891.

5 • Woo A, Rakowski H, Liew JC, *et al*. Mutations of the beta myosin heavy chain gene in hypertrophic cardiomyopathy: critical functional sites determine prognosis. Heart 2003; 89:1179–1185.
This is a cohort study of HCM patients with the beta MHC genetic defect and their family members, noting heterogeneity of disease expression based on the type of genetic mutation.

6 Jongbloed RJ, Marcelis CL, Doevendans PA, *et al*. Variable clinical manifestation of a novel missense mutation in the alpha-tropomyosin gene in familial hypertrophic cardiomyopathy. J Am Coll Cardiol 2003; 41:994–996.

7 •• Maron BJ, McKenna WJ. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2003; 42:1687–1713.
This consensus document provides a comprehensive clinical treatment algorithm for the treatment of children with HCM, and addresses topics of controversy including the role of pacemaker management, implantable cardiac defibrillators, and alcohol septal ablation.

8 • Tsybouleva N, Zhang L, Chen S, *et al*. Aldosterone, through novel signaling proteins, is a fundamental molecular bridge between the genetic defects and the cardiac phenotype of hypertrophic cardiomyopathy. Circulation 2004; 109:1284–1291.
This report explores the clinical question of genetic heterogeneity with an emphasis on aldosterone as a potential modulator in disease expression.

9 Charron P, Heron D, Gargiulo M, *et al*. Prenatal molecular diagnosis in hypertrophic cardiomyopathy: report of the first case. Prenat Diagn 2004; 24:701.

10 • McMahon CJ, Nagueh SF, Pignatelli RH, *et al*. Characterization of left ventricular diastolic function by tissue Doppler imaging and clinical status in children with hypertrophic cardiomyopathy. Circulation 2004; 109:1756–1773.
This is the first study to demonstrate abnormalities on tissue Doppler imaging in children with HCM, and to relate these abnormalities with other clinical variables.

11 Konno T, Shimizu M, Ino H, *et al*. Diagnostic value of abnormal Q waves for identification of preclinical carriers of hypertrophic cardiomyopathy based on a molecular genetic diagnosis. Eur Heart J 2004; 25:246–251.

12 Monserrat L, Elliot PM, Gimeno JR, *et al*. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol 2003; 42:873–879.
This report describes the identification of a new marker of sudden death risk for young patients with HCM.

13 • Drinko JK, Nash PJ, Lever HM, Asher CR. Safety of stress testing in patients with hypertrophic cardiomyopathy. Am J Cardiol 2004; 93:1443–1444.
Many physicians fail to perform cardiopulmonary stress tests on children with HCM due to fear of adverse events. This paper demonstrates the safety of stress testing in a large number of patients with HCM.

14 Amano Y, Takayama M, Takahama K, Kumazaki T. Delayed hyper-enhancement of myocardium in hypertrophic cardiomyopathy with asymmetrical septal hypertrophy. Comparison with global and regional cardiac MR image appearances. J Magn Reson Imaging 2004; 20:595.

15 Sorajja P, Ommen SR, Nishimura RA, *et al*. Myocardial bridging in adult patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2003; 99:889–894.

16 • Downar J, Williams WG, McDonald C, *et al*. Outcomes after unroofing of a myocardial bridge of the left anterior descending coronary artery in children with hypertrophic cardiomyopathy. Pediatric Cardiol 2004
This is a follow-up paper of children with HCM and surgical myectomy of myocardial bridges of epicardial coronary arteries. Myocardial bridging has been suggested to be a cause of ischemia and an important risk factor for sudden death in children with HCM, and these authors provide evidence in a small case series of resolution of symptoms with unroofing.

17 Cecchi F, Olivotto I, Gistri R, *et al*. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med 2003; 349:1027–1035.

18 • Maron BJ. AHA Scientific Statement. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. Circulation 2004; 109:2807–2816.
This comprehensive panel statement summarizes the current recommendations for physical activity in children with HCM, long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular dysplasia, and Marfan syndrome.

19 • Minikata K, Dearani JA, Nishimura RA, *et al*. Extended septal myectomy for hypertrophic cardiomyopathy with anomalous mitral papillary muscle and chordae. J Thorac Cardiovasc Surg 2004; 127:481–489.
This report deals with the difficult topic of how to surgically address left ventricular outflow tract obstruction when the mitral valve apparatus is an integral part of the obstruction, and provides an alternative treatment strategy to mitral valve replacement.

20 •• Alexander MF, Cecchin F, Walsh EP, *et al*. Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. J Cardiovasc Electrophysiol 2004; 15:77–78.
This retrospective review documents a high incidence of complications in children who have had an implantable cardiac defibrillator.

21 • Begley DA, Mohiddin SA, Tripodi D, *et al*. Efficacy of implantable cardioverter defibrillator therapy for primary and secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Pacing Clin Electrophysiol 2003; 26:1887–1896.
This report outlines survival rates and therapeutic implantable cardiac defibrillator intervention-free rates for patients receiving a defibrillator for primary prevention or secondary prevention, and notes a higher rate of therapeutic implantable cardiac defibrillator intervention in patients aged less than 21 years.

22 • Luedemann M, Hund K, Stertmann W, *et al*. Implantable cardioverter defibrillator in a child using a single subcutaneous array lead and an abdominal active can. Pacing Clin Electrophysiol 2004; 27:117–119.
This report describes a novel alternative to epicardial patches for implantable cardiac defibrillator placement in a small child.

23 Kuhn H, Seggeweiss H, Gietzen FH, *et al*. Catheter-based therapy for hypertrophic cardiomyopathy. First in-hospital outcome analysis of German TASH registry. Z Kardiol 2004; 93:23–31.

24 Aroney CN, Goh TH, Hourigan LA, Dyer W. Ventricular septal rupture following nonsurgical septal reduction for hypertrophic cardiomyopathy: treatment with percutaneous closure. Catheter Cardiovasc Interv 2004; 61: 411–414.