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Innovation Associated with the Management and Treatment of Children with Hypertrophic Cardiomyopathy – a Review of the Current Literature

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Abstract: Primary hypertrophic cardiomyopathy (HCM) is a common inherited abnormality in children and adults, and is known to be associated with genetic predisposition. Disease can be present in childhood, adolescence or adulthood. It is a frequent cause of disability and death in those of all ages. Indeed, it is the most common cause of sudden death in the young athlete. Typical symptoms include dyspnea, chest pain, palpitations, and syncope. The diagnosis is usually suspected on clinical examination and confirmed by imaging. Some patients are at increased risk of sudden cardiac death, heart failure, and atrial fibrillation. Patients with an increased risk of sudden cardiac death undergo cardioverter-defibrillator implantation; in patients with severe symptoms related to ventricular obstruction, septal reduction therapy (myectomy or alcohol septal ablation) is recommended. Life-long anticoagulation is indicated after the first episode of atrial fibrillation. In this review we concentrate on the so-called sarcomeric forms of HCM. The non-sarcomeric forms of the disease are both phenotypically and genetically different from the group to be discussed.

Key words: Left ventricular hypertrophy, Hypertrophic cardiomyopathy, Sudden cardiac death, Septal myectomy

1. History

The first case of hypertrophic cardiomyopathy (HCM) is generally considered to have been described by Schminke in 1907. Already in the 19th century, however, there were reports in the German and French literature of specimens with the gross aspect of what we now recognize as HCM (Meershwan,1968; Ten Cate, 1978). It was the publications of Brock 1957, Teare 1958 and Bercu 1958 nonetheless, that focused on the clinical and pathological aspects of this disease and that set the scene for an era or waxing interest in HCM (Brock, 1957; Teare, 1958; Bercu, 1958). From the historical point of view, it is of interest that Berheim, in 1910, described a syndrome of right heart failure in patients with left ventricular hypertrophy of diverse origin (Berheim, 1910).

Over recent years, our knowledge has evolved enormously, mainly though advances in molecular genetics and understanding pathophysiological mechanisms, as well as our awareness of the great variability in its expression. HCM is now recognized as a genetic cardiac disease with an autosomal dominant pattern of

inheritance, but with variable penetrance and expression albeit that sporadic case occurs (Maron, 2004; Ramush, 2020).

HCM in childhood is a heterogeneous disease with variable progression. Disease have 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, and especially to its unsatisfactory response to standard anti-failure therapy (Watkins,1992). Reports have mostly come from tertiary centers, raising the possibility of a selection bias in favor of the very sick children. Unfortunately, still now reports from Balkans countries of the disease are scanty.

Prevalence of the hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is one of the more common genetic cardiac condition, having a prevalence of 1 in 500 of the population at –large. Included within this number are patients who have no symptoms, as well as those who are at risk for sudden cardiac death. Those with non-sarcomeric disease present with concentric left ventricular hypertrophy, and are associated with syndromes such as Pompe's syndrome, Fabry's and Noonan's syndromes, many of which are storage disease are else representing different genetic abnormalities. For these reason, we confine our discussions to the sarcomeric variants.

Genetics

The sarcomeric form of HCM is genetically inherited in a dominant fashion. It is associated with mutations in any of the gens that are involved with the proteins of the sarcomere. These include many of the components of the thick and thin filaments of the sarcomere (Watkins, 1992). Though many specific mutations have been uncovered, a direct relationship has yet to be determined between specific mutations and phenotypic presentations and prognosis. A large number of the cases involve mutations in either the beta myosin heavy chain, cardiac troponin T, or the myosin binding protein. Mutations in the gens that encode for the other components of the contractile apparatus make up a smaller number of the cases. There is genetic heterogeneity, with more than one gene being associated with the clinical condition. There is also great phenotypic variability, not only among unrelated families, but also within the same family (Ganame, 2008).

The identification of these genetic mutations has led to interest in the development of DNA-based genetic testing of patients in order to aid in their diagnosis and management, as well as the screening of their families. While genetic testing is currently commercially available, its value is not steel clear. There are certainly circumstances where genetic testing for HCM is useful (Colan, 2007). The clinical use of such genetic testing in other clinical situations nonetheless remains to be defined.

In conclusion, there is genetic heterogeneity, with more than one gene being associated with the clinical condition. There is also great phenotypic variability, not only among unrelated families, but also within the same family.

Pathology

The disease is characterized by excessive of the myocardium, often asymmetric in nature, with a preference for the ventricular septum and the adjacent anterior free wall. In most cases, gross inspection will reveal a markedly narrowed left ventricular surface overlying the zone of septal hypertrophy is usually slightly thickened, from fibrosis, and is often shaped as an imprint of the facing aortic leaflet of the mitral valve. In other cases, the hypertrophy can be more diffuse in nature, affecting the greater part of the left ventricular musculature. In rare instances, the disease may affect only the left ventricular apex or the right ventricular free wall. Likewise, systolic anterior motion of the mitral valvular apparatus is often considered an important feature of the disease.

Pathohistology

Extensive myocardial disarray is an important microscopic feature of HCM (Teare, 1958; Maron, 2004). This particular histological texture in isolation nonetheless is far from pathognomonic. Microscopical examination usually reveals disorganization of the myocardial fibres. Small and broad bundles of fibres form an intricate lace-work, often with an abundance of perpendicular junctions of individual cells (Figure 1). The extent of this unusual architecture may vary but, in classical cases, it is extensive, involving the full thickness of the septum or the affected ventricular free wall. Fibrosis may accompany the myocardial disorganization, and thickening of the walls of intramural coronary arteries can occurs. It is as yet speculative whether the abnormalities in fibral arrangement of the myocardial fibres are responsible for the abnormal myocardial compliance encountered in HCM. The marked variability in degree and extent of the changes, however could explain wide spectrum of clinical signs and symptoms. Ventricular hypertrophy is the characteristic finding despite the great genotypic and phenotypic variability. The pathophysiological consequences of the myocardial abnormality are variable; hence the clinical sign and symptoms are varied. The dominant pathophysiological abnormality is impairment of relaxation. The abnormality of diastolic function can result in elevation of the left ventricular end-diastolic pressure, with resulting pulmonary contestation and dyspnea. This is the most common symptom in HCM, particularly when the condition presents in early infancy. Similar elevations of atrial pressures occur in the right side of the heart when the right ventricle is also affected by myocardial hypertrophy. Several studies has shown that the diastolic abnormalities are exceeding complex and may vary from one patient to another, as well as from one moment to the other in the same patient.

Probably of less importance than the diastolic abnormalities producing “inflow obstruction” is the presence of obstruction of the outflow tract, which occurs in some patients. This underscores the obstructive versus non-obstructive forms. The obstruction to either outflow tract has a dynamic characteristic. In the left ventricle, the hypertrophied ventricular septum typically bulges toward, and potentially narrows, the subaortic outflow tract. The distal portion of the mitral valvar apparatus is seen to move anteriorly across the outflow tract during ventricular contraction, making contact with the ventricular septum in mild-systole, a finding known as “systolic anterior motion” (Maron, 2004).

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a b

Figure 1. Disorganized (a) and normal cell pattern (b)

Diagnosis

Hypertrophic cardiomyopathy, in its classic and most common form, is associated with hypertrophy of the left ventricle, most notably the ventricular septum (Bos, 2009). The morphologic, hemodynamic, and clinical manifestations of the disease can vary widely.

Hypertrophic cardiomyopathy 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.

Hypertrophic cardiomyopathy 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, hyperthyroidism, catecholamine secreting tumors, etc. (Bos, 2009). It is the most common inherited cardiovascular disease, with diverse etiology, affecting populations worldwide and the leading cause of sudden cardiac death in young people. Sarcomeric gene defect 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 cardiospeciphic disorders. It is common to group these diseases as familial, syndromic, neuromuscular, and metabolic (storage disease and mitochondrial disorders) (Morita, 2008).

Depending on the site and extent of muscular hypertrophy, patients can develop any combination of obstruction of the left ventricular outflow tract, diastolic dysfunction of the left ventricle, myocardial ischemia, and mitral regurgitation. Cross sectional echocardiography is the mainstay of diagnosis, and typically shows the extent of ventricular hypertrophy.


1

2

Four chamber view of the concentric form of HCM and long axis view of the asymetric form of HCM (Abrevation: RA-right atrium, LA-left atrium, RV-right ventricle, LV- left ventricle, MV-mitral valve**)**

Making the diagnosis of HCM implies that alternative causes of left ventricular hypertrophy, such as systemic hypertension or aortic stenosis, have been ruled out. There are different morphologies of HCM as defined by echocardiography. Asymmetric septal hypertrophy, both in its obstructed or non-obstructed forms, accounts for four-fifths of the cases (Figure 2). The concentric form of HCM sometimes is difficult to differentiate from so-called athlete's heart make up about one-sixth of cases, while the patients with apical hypertrophy account for 3% of cases (Figure 1). The mild-ventricular form makes up the remaining 1-2 % of cases (Bos, 2007).

Extensive physical training can result in significant left ventricular hypertrophy, and can produce the so called athletic heart syndrome. This can be difficult to differentiate from HCM. Additional findings supporting the diagnosis of the athletic heart syndrome include dilatation of the left ventricular cavity, absence of left atrial enlargement, absence of electrocardiographic evidence of left ventricular diastolic abnormalities, absence of a family history of HCM, and a maximum consumption of oxygen of 50 ml/kg minute (Maron, 1999). A decrease in left ventricular hypertrophy associated with deconditioning is definitive evidence for the athletic heart.

The degree of mural thickens can be markedly variable in those with HCM, ranging from mild to massive. In children, the thickness can also change with time. Left ventricular remodeling can occur as children grow, (Maron, 1983; Maron, 2009) such that dramatic increases in left ventricular mural thickness can develop during adolescence in those who initially showed minimal hypertrophy. This phenomena has implications for the utility of echocradigraphic screening of children of family members with known HCM, and underscores the importance of serial studies. Genetic testing, as discussed previously, may also impact on this situation.

Asymmetric ventricular hypertrophy, as already emphasized, is the commonest form of HCM and may be obstructive or non-obstructive. Basal septal hypertrophy typically narrows the left ventricular outflow tract, with systolic anterior motion of the aortic leaflet of the mitral valve potentiating the obstruction, and also resulting in mitral regurgitation. The obstruction may be latent and variable, and is influenced by preload, afterload, and inotropic state. The gradient measured across the outflow tract has shown to be an independent determinant of progressive cardiac failure and functional disability in adults (Rawlins, 2009). Such obstruction is associated with an increase in left ventricular pressure and mural stress, an increased myocardial consumption of oxygen, and myocardial ischemia. Because of the variable dynamic nature of the obstruction, a gradient measured at a single point in time must be interpreted cautiously an in its appropriate clinical context. Identification of a gradient, nonetheless, justifies intervention for its reduction.

The presence of diastolic dysfunction and impaired filling of the left ventricle in HCM have been well documented. In addition, the role of echocardiographically measured diastolic parameters in early detection of the disease, as well as stratification of risk for those known to have HCM, is currently under investigation.

A burgeoning role is now being recognized for other imaging modalities such as cardiac magnetic resonance imaging. This technic has been used to quantify delayed enhancement and scarring, and to determine the coronary arterial flow reserve (Maron, 2004). Its value in guiding the prognosis and management of patients with HCM, in recent publication shows high level of sensitivity.

2. Clinical profiles

While many children with HCM are asymptomatic, some typical 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 usually normal or hypercontractile left ventricular function, with or without obstruction of the left ventricular outflow tract. While, significant obstruction causes symptoms, there are also asymptomatic patients who do not have obstructed outflow tract. In this setting, symptoms are due to factors such as diastolic dysfunction, mitral regurgitation or microvascular dysfunction. The hemodynamic consequences of significant diastolic dysfunction in those with HCM are well known. Because of the associated abnormalities of left ventricular diastole and filling, both the left ventricular end-diastolic and left atrial pressure are elevated, with a concomitant reduction in stroke volume and cardiac output. Chest pain if present, is likely secondary to severe ventricular hypertrophy with myocardial ischemia due to microvascular dysfunction, and can also contribute to worsening cardiac failure (Maron, 2004).

A second well recognized group is made up of the patients with atrial fibrillation and its complication, such as embolic stroke. It is uncommon, however, to find children in this group, as it is uncommon to find them with end-stage-systolic and diastolic dysfunction (Maron, 2004).

The final group with a typical clinical profile is made up of those who are at risk for sudden cardiac death. Those filling in this important group will be discussed later. In and unselected population of patients with HCM the incidence of sudden death is around 1% each year (Bos, 2009; Maron, 1999). Given the lower incidence of sudden death from all causes in young patients compared to adults, however, HCM accounts for a significant percentage of sudden death in children.

The mechanism of sudden death in this setting is thought to be the sudden onset of a malignant ventricular arrhythmia. The notion has been confirmed by electrographic recordings of appropriate discharges obtained from patients with implanted defibrillator. Polymorphic ventricular tachycardia or ventricular fibrillations are more commonly seen compared to monomorphic ventricular tachycardia. This is not surprising, as the substrate for these arrhythmias is severe diffuse hypertrophy with disarray of the suggested myocytes, along with ischemic-induced myocardial necrosis and fibrosis. Intense exercise, by increasing the demand for oxygen, and worsening obstruction across the outflow tract, and decreased coronary perfusion due to peripheral vasodilatation, are common triggers, albeit that in many instances no obvious trigger is identified.

Management of symptoms

Hypertrophic cardiomyopathy is a complex disease with variation in presentation, symptoms, severity, and response to therapy. The goals of the therapy in HCM are symptom control and prolongation of survival. Symptoms such as chest pain, dyspnea, and exercise intolerance can often be managed medically, and surgery has been successful in certain patients groups [8]. 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 over time, this goal still remains elusive (Watkins, 1992).

Contrary to recent progress in treatment children with HCM therapy based on the use of beta-blockers, Calcium channel blockers, antiarrhythmic drugs (Disopyramide, Amiodarone), pacemaker therapy (asynchronous ventricular pacing), implantation of the intracardiac defibrillator, and in extremely severe forms surgical myectomy and percutaneous radiofrequency septal reduction (Colan, 2007). Our account of HCM based on experience in a national referral center in Prishtina 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. Also, these figures raise the very important question on why the standard medical treatment of the disease is so frequently unsatisfactory.

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 hyper contractile left ventricular function, with or without obstruction of the 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 (Ganame, 2008).

A second well recognized group is made up of the patients with atrial fibrillation and its complications, such as embolic stroke. The final group with a typical clinical profile is made up of those who are at risk for sudden cardiac death (Brock, 1957).

Hypertrophic obstructive cardiomyopathy is an uncommon cause of left ventricular outflow tract 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 (Maron, 2004). Transthoracic and transesophageal Doppler echocardiography is a gold standard to document the degree of myocardial septal hypertrophy and the resting gradient across the left ventricular outflow tract.

Identifying the risk factors for sudden death

Given the annual incidence of 1% for sudden death, identification of those patients at risk is challenging. Factors contributing to increased risk include a family history of sudden death, syncope, especially when exertional, repetitive nonsustained ventricular tachycardia, exercise-induced hypotension and extreme left ventricular septal hypertrophy. It is unclear in children whether indexed or absolute measurements of mural thickness should be used to asses risk. This is an issue of considerable importance, since extreme hypertrophy may be the most important risk factor for sudden death. Although it may contribute to symptoms and further progression of left ventricular hypertrophy there is no evidence that the degree of obstruction across the left outflow tract contributes directly to the risk for sudden death (Maron, 2009).

Medical therapy

There are many important caveats regarding medical therapy in patients with HCM. Firstly, medical therapy has not been shown to alter prognosis, being focused primarily on the relief of symptoms. There are no large randomized trials on which to base therapeutic strategies, which hence are based on observational data and clinical experience. Because every patient is different, an empiric approach to therapy is critical.

If there are exertional symptoms of cardiac failure, the initial therapy typically includes negative inotropic agents, usually beta-blockers, verapamil or disopyramide. The mechanisms of benefits include slowing of the heart rate, and prolongation of the diastole, which allows for an increase in ventricular filling. These agents potentially relieve the symptoms of an obstructed left ventricular outflow tract, since they have a

negative inotropic effect, but often do not have a significant impact on reducing the degree of obstruction. Beta-blockers may relieve anginal symptoms by decreasing myocardial demand for oxygen, while blockers of the calcium channels, such as verapamil, may reduce angina by their beneficial effects on microvascular dysfunction. A beta-blockers or verapamil is typically used first, and is titrated until symptoms improve, or until side effects appear. If this strategy is unsuccessful, then another drug should be considered. In the presence of an obstructed left ventricular outflow tract, beta-blockers are preferred because of the undesirable effects of verapamil on the systemic vascular resistance.

Beta-blockers are usually the initial drug chosen for medical therapy. Whether short or long acting agents are selected is at the discretion of the cardiologist. Side-effects in children include depression, impaired performance at school, and untoward effects on growth and development. There are beneficial effects of dysopiramide in the presence of severe symptomatology due to an obstructed left ventricular outflow tract, although the anticholinergic side effects limit its use (Maron, 2009). Because disopyramide can accelerate atrioventricular nodal conduction, it should be ised in conjunction with a beta-blocker. There is little data, however, on either its use or dosage in children. It is usually used in patients with mild or absent obstruction of the left ventricular outflow tract, and is usually well tolerated, but may be associated with side-effects that include sinus arrest, atrioventricular block and pulmonary oedema.

In patients with severe obstructive HCM several classes of medications are contraindicated or else should be used with great caution. Vasodilators decrease the systemic vascular resistance, worsen the obstruction in the left ventricular outflow tract, and exacerbate symptoms. Diuretics may be used cautiously in patients with persistent heart failure and volume overload, albeit that dehydration and a critical reduction in preload can worsen symptoms. Digoxin and other positive inotropic agents should be avoided since they worsen any obstruction of the left ventricular outflow tract. As already discussed, medical therapy is generally unsuccessful in reducing the resting gradient across the left ventricular outflow tract. Its major role is to reduce symptoms.

Medical therapy is controversial in the asymptomatic patient with HCM. Most clinicians would choose not to institute medical therapy for those without symptoms. Exceptions include those with clinical and morphological features known to put them at an increased risk, for example, patient with massive hypertrophy or severe obstruction of the left outflow tract in the absence of symptoms. More often than not, however, the patients making up the latter group with massive hypertrophy or severe obstruction of the left outflow tract are likely to have some degree of symptomatology.

Prevention of sudden death

Given the dismal outcome for patients suffering cardiac arrest out of hospital, primary prevention of sudden death offers the best chance of improving survival. The low frequency of occurrence in a relatively uncommon disease with the risk of sudden death spread over many years has precluded the ability of prospective randomized trials to assess the efficacy of any treatment. The prolonged period of risk also implies that the patient is also exposed for a prolonged period to the potential detrimental effects of the chosen therapeutic modality. Use of beta blockers has shown a modest reduction in sudden death in a diverse group of cardiac diseases, especially ischemic heart disease. Given their long-term safety profile, use of the beta-blockers appears justified in preventing sudden death in those with HCM. Indeed, one retrospective report showed no sudden death in children receiving high dose of beta blockers (Maron, 2009). The topic nonetheless, is controversial. In the limited experience available from patients having appropriate discharges from implantable cardioverter defibrillators, many were receiving beta blockers or amiodarone, thus providing indirect evidence of lack of efficacy of antiarrhythmic therapy. Amiodarone is probably the most rigorously of all the antiarrhythmic drugs in those with both ischemic and non-ischemic substrates. A small but consistent reduction in arrhythmic sudden death has been offset by increase in mortality due to its systemic toxicity (Maron, 2004; Maron, 2009; Poutanen, 2006).

Retrospective studies in the primary prevention of sudden death with the implantable cardioverter defibrillator in HCM have shown that appropriate chocks are effective in terminating spontaneously occurring episodes of ventricular tachycardia or ventricular fibrillation that would presumably, have

resulted in sudden death. Implantation of cardioverter defibrillator however is far from ideal, especially in children, in whom a substantial number of device related complications, including inappropriate shock, dislodgment of fracture of leads, malfunctions of the device, and infections have been reported. In addition, it can be difficult to place either endocardial or epicardial devices in small children. In the absence of any other effective therapy, nonetheless, implantation of a cardioverter defibrillator should be considered to be the mainstay of therapy for secondary and primary prevention of sudden death (Sotgia, 2008; Sherrid, 2005; Koffland, 1993).

Septal myectomy in obstructive hypertrophic cardiomyopathy

Left ventricular septal myectomy is the gold standard for treatment of patients with severe symptoms due to obstructive HCM that are unresponsive to medical therapy Cairns, 1997; Julian, 1997). While the early surgical experience was associated with complications of complete heart block, production of ventricular septal defects, injury to the aortic or mitral valves, and incomplete relief of obstruction, this is uncommon in the current era. The transaortic approach remains the primary method of extended left ventricular septal myectomy. A decrease in the gradient is accomplished by physical enlargement of the outflow tract, and by interruption the pathophysiological sequence of events, primarily systolic anterior motion of the aortic leaflet of the mitral valve, which are responsible for the obstruction (Moss, 1996). Complete relief of the obstruction by septal muectomy also eliminates the mitral regurgitation caused by the systolic anterior motion of the mitral valve leaflet. Residual mitral regurgitation after adequate myectomy is usually due to intrinsic mitral valve pathology, for example, ruptured cords, prolapse of leaflets, or annular dilatation. These can be corrected by direct and appropriate valvar repair. Replacement of the mitral valve is reserved for patients with primary pathology that is not amenable to repair.

Indication for surgery

Symptoms of dyspnea, chest pain, pre-syncope, syncope, fatigue, and orthopnea or paroxysmal nocturnal dyspnea may result from an obstructed left ventricular outflow tract. Despite appropriate adjustment of medications, symptomatic relief can be incomplete, transient or accompanied by intolerable side-effects. In such patients, septal myectomy is the preferred treatment when the resting or provocable gradient is greater than 50 mmHg (Silka, 1993). Surgery may also be advised in children who are asymptomatic, or mildly symptomatic with gradients of between 75 and 100 mmHg at rest. In these patients, the operative risk is around 1% and relief of obstruction is predictably good. Importantly, surgery for obstructive HCM especially for children should be confined to centers with significant volume, and with known risk of mortality of no more than 1-2 %.

Surgical technique

Over the last 3 decades septal myectomy has evolved from the classic myectomy to a more extended left ventricular septal myectomy (Nishimura, 1996). Intraoperative transoesophageal echocardiography is used routinely to evaluate the anatomy and thickness of the septum, and mitral valve function. Intraoperative transoesophageal echocardiography is used routinely to evaluate the anatomy and thickness of the septum and mitral valvar function. Standard median sternotomy is performed and intracardiac pressures are measured directly in the left ventricle and aorta. If the measured gradient is less than 30 mmHg because of the conditions of anesthesia, provocation with isoproterenol is performed to determine the maximal gradient. Exposure is via an aortotomy. Visualization of the ventricular septum is facilitated by posterior displacement of the left ventricle with forceps. The septal incision is begun at the base of right aortic sinus and continued leftwards the mitral valve and apically to the bases of the papillary muscle. Resection of the apical third of sinus is then performed, effectively making a much wider through at the midventricular level. The methods of extended myectomy as described can be difficult in children when the orifice of the aortic valve is small. For all these reasons, minimally invasive techniques, for example robotics, are not used in this setting. The most common reason for residual obstruction is incomplete extension of the septectomy toward the middle of the left ventricle. In general, bypass would be resumed for resection if the gradient were from 15 to 20 mmHg, or if there was persistent systolic anterior motion of the aortic leaflet of the mitral.

Outcome of septal myectomy

Symptomatic children with obstructive HCM have a higher annual rate of death, at 6%, compared to adults (Theodoro). Although the operation is technically more challenging because of the difficulty of exposure of the smaller structures, there is a role for surgery in children. Experience with left ventricular myectomy at the Mayo Clinic now exceeds 2000 patients.

As we have discussed, obstruction within the left ventricular outflow tract has been found to be a strong independent predictor of progression to severe cardiac failure, stroke, and the relative risk of death (Maron, 2011). Whether relief of obstruction by septal myectomy also prolongs life has been an important but largely unresolved issue, due to the impracticality and ethical considerations involved in designing a controlled trial comparing patients randomized to surgery and other treatments. Previous reports and a recent large retrospective and controlled analysis in adult patients suggest that myectomy results in excellent long-term survival and may improve natural history of the disease. After septal myectomy long-term actuarial survival was 99%, 98% and 95%, at 1, 5 and 10 years, respectively, when considering mortality related to HCM. This survival did not differ from that expected in a matched general population in the USA. It was superior to that achieved in patients with HCM and obstructed left ventricular outflow tracts not submitted to surgery (Maron, 2003). Furthermore, myectomy was also associated with reduced long-term risk for sudden cardiac death. These findings were noted in adult patients. Larger numbers of children undergoing myectomy are required before a similar analysis can be performed to assess the benefits in childhood. Surgical myectomy, furthermore, does not eliminate the need to assess the risk of each patient for sudden cardiac death. Nor does it eliminate the need to consider implanting a cardioverter defibrillator in those with significant burden of risk, such as those with a positive family history of sudden cardiac death, "massive" left ventricular hypertrophy, non-sustained ventricular tachycardia, and so on.

Although the basic transthoracic approach for performing a septal myectomy has been known for over 40 years, the operation remains technically challenging and the results are dependent on the skill of the surgeon. While myectomy can be performed successfully in children, and even in infants, adequate resection may be compromised by small size of the aorta and limited visibility of the medioventricular region. Poor visualization of the anatomy bellow the aortic valve can result in injury to the oartic or mitral valves, while incorrect placement of incisions, or excessive muscular resection or traction can produce heart block or a ventricular septal defect. These limitations account in part for the need for the reoperation at a later age for some children (Dearani, 2004).

Septal myectomy, nonetheless, effectively relieves obstructed left ventricular outflow tracts and cardiac symptoms in both adults and children with obstructive HCM. In experienced centers operative mortality for isolated myectomy in both children and adults is low, and late results continue to improve. Children are more likely to need reoperation when complete elimination of the gradient cannot be achieved at the initial operation because of difficulties in exposure, or because of ventricular remodeling resulting in recurrent obstruction.

Cardiac transplantation

Currently, cardiac transplantation is the ultimate surgical resort for patients who do not respond to medical or surgical treatment. But the option is available only in relatively few centers, most of them in United States of America and in Europe. 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 (Minakata, 2005). 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 (Maron, 2004).

Screening for HCM

Based on the data of the high incidence of HCM and often cause of the sudden death some countries have applied screening for HCM as routine examination. 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 left ventricular hypertrophy develops) or in the clinical stage (after left ventricular hypertrophy 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 (Figure 1). More complex interventions such as cardiac magnetic resonance imaging, biomarkers, and genetic analyses may be appropriate for diagnosis and care in specific cases. The best application of these many modalities is yet to be determined, and will doubtless vary between location, population and availability (McCully, 1996).

3. Conclusion

Hypertrophic cardiomyopathy (HCM) is an important disease affecting populations worldwide. It is the most common inherited cardiovascular disorder and the leading cause of sudden death in young people. Several community-based epidemiologic studies have estimated the risk of sudden cardiac death in teenagers and young adults with HCM to be approximately 1 % per year [36]. Associated risk factors for sudden cardiac death include: a family history of HCM related premature death, unexplained syncope, a hypotensive or attenuated blood pressure response to exercise, recurrent no sustained ventricular tachycardia and massive left ventricular hypertrophy (a wall thickness > 3 cm). The prevalence of HCM has been estimated to be at most 0.2 % in the United States, affecting about 1 of every 500 adults.

HCM is a complex disease with variation in presentation, symptoms, severity, and response to therapy. In figure 4 we summarize the options for treatment, providing in our opinion a reasonable approach to the care of children and adolescents with this disease.

Management of symptoms

Hypertrophic cardiomyopathy is a complex disease with variation in presentation, symptoms, severity, and response to therapy. The goals of the therapy in HCM are symptom control and prolongation of survival. Symptoms such as chest pain, dyspnea, and exercise intolerance can often be managed medically, and surgery has been successful in certain patients groups (Sieler, 1991; Ramush, 2020). 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 over time, this goal still remains elusive (Ommen, 2005).

Contrary to recent progress in treatment children with HCM therapy based on the use of beta-blockers, Calcium channel blockers, antiarrhythmic drugs (Disopyramide, Amiodarone), pacemaker therapy (asynchronous ventricular pacing), implantation of the intracardiac defibrillator, and in extremely severe forms surgical myectomy and percutaneous radiofrequency septal reduction (Minaka, 2004).

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 hyper contractile left ventricular function, with or without obstruction of the 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 (Colan, 2011).

A second well recognized group is made up of the patients with atrial fibrillation and its complications, such as embolic stroke. The final group with a typical clinical profile is made up of those who are at risk for sudden cardiac death (McCully, 1996).

Hypertrophic obstructive cardiomyopathy is an uncommon cause of left ventricular outflow tract 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 (Maron, 1996). Transthoracic and transesophageal Doppler echocardiography is a gold standard to document the degree of myocardial septal hypertrophy and the resting gradient across the left ventricular outflow tract.

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