

Review Article

Hypertrophic Cardiomyopathy in Children, Teenagers and Young Adults

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Hypertrophic cardiomyopathy (HCM) is a rather common hereditary disease and is a significant cause of disability and death in patients of all ages. Sudden death, which is the most serious element of the natural history of the disease, is particularly common in teenagers and young adults.^{1,2} Accordingly, we believe that a review of the most recent data related to the natural history, prognosis, and treatment of HCM during childhood and teenage years would be of value.

HCM is the most common hereditary cardiovascular disease, with an incidence in the general population that reaches 0.2% worldwide.³⁻⁵ However, a significant proportion of those patients, despite carrying the gene, are not diagnosed clinically, with the result that the disease accounts for less than 1% of the cases in a normal cardiology outpatients' clinic.⁶

HCM heritability has an autosomal dominant character and is caused by mutations on at least 10 genes that code for proteins of the cardiac sarcomere. Most common are the mutations on the genes that code for the beta-myosin heavy chain, troponin T and protein C. Because of intra-gene polymorphism (more than 200 mutations have been reported), the use of genetics in everyday clinical practice is extremely limited.^{3,7,8}

The diagnosis of HCM is based on the echocardiogram,^{9,10} which demonstrates

the hypertrophic but not dilated left ventricle in the absence of other disease that could cause hypertrophy (e.g. arterial hypertension, aortic stenosis). The clinical examination is not a reliable method for diagnosis, because the majority of patients, especially the young, do not show obstruction of the left ventricular outflow tract and thus have no detectable murmur. It is interesting that 10% of young patients with HCM are identified during a check up prior to sporting activities. In contrast to the clinical examination, the ECG is pathological in 75-95% of patients,^{11,12} showing a great variety of disturbances, such as a high R in the left precordial leads, a deep S on the right, and diffuse repolarisation abnormalities (mainly negative T waves). The ECG and echocardiographic disturbances usually become apparent during the teens and in the majority of cases the phenotypic manifestation of the disease is complete by the age of 21 years.^{9,13} Thus, it is not uncommon for children of pre-teen age (<12 years) to be carriers of the disease without having developed the characteristic morphological features (left ventricular hypertrophy) on which the diagnosis is based.

One very interesting and often insoluble problem is the differential diagnosis between HCM and the normal hypertrophy that is seen in some high-performance athletes.¹⁴ Athletes who train for a long period at championship level exhibit a physiologi-

cal thickening of the cardiac walls as part of their adaptation to the demands of intensive exercise. In some sports particularly, such as long-distance running, swimming, cycling and rowing, this physiological hypertrophy is more significant and more common. The following points can help in the differential diagnosis:

- In athletes the hypertrophy is usually symmetrical.
- When the hypertrophy affects only the interventricular septum it usually does not exceed 12-13 mm, while in HCM it is usually ≥ 16 mm.
- In only 2% of athletes has an interventricular septum thickness >13 mm been found, and that referred exclusively to those engaged in cycling or rowing.
- No sportswoman has ever been found to have an interventricular septum thickness >13 mm.
- The ECG in HCM usually has deep Q and negative T waves.
- On the echocardiogram of the “athlete’s heart” the left ventricular end-diastolic diameter is usually >55 mm, while in HCM patients it is <45 mm.
- On mitral Doppler in HCM the ratio of early (E wave) to atrial (A wave) flow is usually <1 .
- On cardiopulmonary exercise testing the peak O_2 consumption in athletes is usually >50 ml/kg/min, or greater than 120% of the predicted rate.

If the above criteria are not sufficient for a sure diagnosis, the only safe solution is the cessation of exercise for 2-3 months, after which time if the hypertrophy was the result of exercise it will have reduced by 2-5 mm.

As mentioned above, the phenotypic manifestations of HCM may be delayed. This has implications for the programming of preventive familial screening (i.e. in families where a first degree relative suffers from the disease). Usually, the hypertrophy becomes apparent during the period of rapid somatic development (age 13-17 years). Cases have been reported, however, of delayed appearance of the hypertrophy (after the age of 21 years), usually due to mutations of the genes responsible for troponin T and binding protein C.^{15,16} For this reason, the strategy for preventive familial echocardiographic screening is as shown in Table 1.¹³

The diagnosis of HCM before the age of 2 years is rare.¹⁷⁻¹⁹ In these few cases it is usually discovered by chance, during the investigation of a murmur. At this age, the hypertrophy of the interventricular septum, apart from obstructing the left ventricular outflow tract, also causes obstruction of the right ventricular outflow tract because of hypertrophy of the trabeculae and auxiliary muscles (*crista supraventricularis*, moderator band). In such cases, it is extremely rare for the disease

Table 1. Familial echocardiographic screening for hypertrophic cardiomyopathy.

<12 years	– Familial history of early sudden death (<45 years) – Athlete in intensive training – Symptoms – Indications (e.g. ECG) of left ventricular hypertrophy
12-21 years	Check up every 12 or 18 months
>21 years	Check up every 5 years

to present with signs of heart failure.¹⁹ However, when some degree of hypertrophy of the left ventricular walls is discovered at young ages (<4 years) further examinations should be performed to rule out other conditions that may cause early ventricular hypertrophy, such as glucagon diseases, mitochondrial diseases, Fabry’s disease, or Noonan’s syndrome. Since the disease appears before the age of 12 years in only a small number of cases, the prognostic significance is still not generally known.

The obstruction of the left ventricular outflow tract is a powerful, independent prognostic factor for the occurrence of heart failure, in both adults and children,²⁰ and for this reason it is important to distinguish between the obstructive and non-obstructive types of the disease. The characteristic clinical finding for obstruction is a systolic ejection murmur that is louder at the apex. The long-term consequences of obstruction are due to an increase in left ventricular pressure and wall stress, myocardial ischaemia, myocyte necrosis and subsequent fibrosis.²¹ It should be emphasised, though, that the obstruction in HCM is dynamic, with the result that the pressure gradient along the outflow tract changes in many and various normal circumstances (e.g. alcohol consumption, rich meals, exercise).

Study of the development and the prognosis of the disease has shown that we can distinguish three subgroups. These are to a large degree independent,²² meaning that a given patient usually belongs to only one subcategory and follows the course that characterises that group. Thus, for example, if someone has risk factors for sudden death, (s)he will not exhibit heart failure, and *vice versa*. The subgroups are as follows: a) patients with high risk of sudden death; b) patients with symptoms of heart failure (dyspnoea, chest pain, easy fatigability); c) patients with atrial fibrillation (very rare in childhood).

Sudden death is the most common cause of mortality in patients with HCM and is undoubtedly the worst and most unpredictable complication of the disease.²³⁻²⁸

The annual mortality for all patients with HCM ranges around 1%. In patients who are at high risk for sudden death it rises to 5%, which means that probably the most important challenge in the management of the disease is the identification of those patients. Sudden death is rare before the age of 12 years and usually occurs in teenagers and young adults (<30 years old), in whom HCM is the most common cause of sudden death during exercise.²⁹ From 10% to 20% of all patients with HCM have one or more of the following risk factors for sudden death:³⁰⁻³²

- A history of cardiac arrest or spontaneous, sustained ventricular tachycardia.
- A family history of early sudden death (<45 years) related with the disease.
- Syncopal episodes, especially during exercise, or when repeated, or when associated with arrhythmias (on Holter monitoring).
- Multiple, repeated episodes of non-sustained ventricular tachycardia on the 24-hour ECG. Such episodes are generally rare in children, but when they are present they dramatically increase the risk of sudden death.³¹
- A drop in blood pressure, or inability to increase it and maintain it at high levels (>25 mmHg above resting level) during exercise testing.³³
- Extreme left ventricular hypertrophy, namely an interventricular septum thickness ≥ 30 mm.³⁴

All these risk factors have a high negative prognostic value, especially in the case of the inability to increase blood pressure during exercise testing. The negative prognostic value of this marker is so high (97%) that when there is no other risk factor the patient can be reassured. Regarding obstruction and its association with sudden death, the existing evidence²⁰ is not strong enough to establish it as a specific factor in prevention strategies. It also appears that, at least until now, using the genotype to determine prognosis is not reliable.³⁵ The induction of tachycardia with programmed ventricular stimulation during an electrophysiological study is not considered to be a risk factor for sudden death³ and is tending to be abandoned. Consequently, based on the above, every young patient with HCM should undergo not only an echocardiographic examination, but also 24-hour ECG monitoring and a stress test with a view to detecting any risk factors for sudden death.

The prevention of sudden death is divided into secondary and primary. In patients who have been resuscitated from an episode of cardiac arrest or who have documented episodes of spontaneous, sustained

ventricular tachycardia (secondary prevention) there is an absolute indication for an implantable cardioverter-defibrillator (ICD), regardless of age, sex, existence of symptoms, or presence of left ventricular outflow tract obstruction.^{36,37} Primary prevention is based on the detection of those patients who are potentially at greatest risk. Each risk factor alone has a low positive prognostic value, around 20%,²⁵ meaning that preventive treatment (ICD or amiodarone) is indicated in those individuals who have two or more risk factors, in whom the annual rate of sudden death reaches 4-5%. When there is only one risk factor, the evidence is not clear and the decision must be made on a case by case basis. Overall, the ICD seems to be superior to amiodarone, and to drugs in general, in terms of efficacy.²³ ICD discharges restored sinus rhythm during a 3-year period in 25% of patients who received one.³⁶ When implanted for secondary prevention, the ICD discharge rate was 11% annually, while for primary prevention the rate fell to 5%. About half the cases where ICD operation was necessary involved children or young adults. In addition, there were cases where the activation occurred after an extremely long time (9 years after implantation). However, the use of ICDs in children is not complication free and is technically clearly more difficult, often requiring abdominal implantation and replacement because of somatic development.^{38,39} For these reasons, when there is an indication for preventive treatment in small children who have not completed their somatic development, some propose the use of amiodarone for a period of time until the patients mature.

The manifestation of symptoms of heart failure (dyspnoea on effort, orthopnoea, paroxysmal nocturnal dyspnoea, easy fatigability) and myocardial ischaemia (chest pain), although rare in children, can occur at any age. In the absence of obstruction, the symptoms of heart failure are due to left ventricular diastolic dysfunction.⁴⁰ Anginal-type discomfort appears to be due to disturbances of the coronary microcirculation.³⁴

Symptomatic therapy aims to reduce symptoms and improve the patient's functional capacity. The choice of appropriate medication is determined by the presence or absence of obstruction. Thus, patients who do not have obstruction receive beta-blockers, verapamil and diltiazem. The beneficial effects of these drugs seem to be achieved by improving diastolic dysfunction and microcirculation disturbances. Traditionally, beta-blockers were the drugs of choice, especially when the dominant symptom was dysp-

noea.³ Calcium antagonists are given when anginal problems dominate the clinical picture, or when beta-blockers prove ineffective. Diuretics should be administered extremely frugally, since there is a risk of haemodynamic deregulation in those patients whose heart failure is due to diastolic dysfunction.

When there is obstruction, then beta-blockers are the drugs of choice, whereas in such cases verapamil should be given with great caution because it may cause peripheral vasodilation and haemodynamic deterioration.⁴¹ Propranolol is given initially in doses of 1.5-3 mg/kg/24h, which are progressively increased to at least 6 mg/kg/24h. In children with bronchospasm metoprolol may be given as an alternative (6-12 mg/kg/24h).

Patients with a severe degree of obstruction, who do not respond to medication or who show non-tolerated side effects from drug administration, are candidates for surgical treatment. The procedure of choice is Morrow myectomy, which is indicated when the symptoms persist in spite of intensive medication and there is a concomitant pressure gradient >50 mmHg.⁴² It is estimated that around 5% of all patients with HCM will be candidates for surgical repair.²² The results in experienced centres are very satisfactory. Mortality ranges from 1-2% and improvement of symptoms is achieved in 70% of patients, for a period of at least 5 years after the procedure.^{3,43} A small, but non-negligible percentage of paediatric cases (10%) can present with restenosis after initially successful surgery, although it seems that the good result persists over time even when the procedure is carried out in patients under 14 years old.⁴⁴ In addition, in paediatric patients the surgery may cause damage to the aortic valve leaflets, necessitating valve replacement.⁴⁵ Surgical myectomy is also indicated in patients with severe and refractory symptoms attributable to the presence of a provocative pressure gradient,³ as well as in those with a very large pressure gradient, above 80-100 mmHg, regardless of the presence or absence of symptoms.

Dual chamber pacing is tending to be abandoned as an alternative method of treatment in children, since the clinical improvement seen is largely attributable to a placebo effect and is not supported by objective findings of improved exercise capacity.⁴⁶ It also presents many technical difficulties⁴⁷ and in addition has been found not to protect against the risk of sudden death. Percutaneous septal ablation⁴⁸ is contraindicated in children and young adults because of its hidden risks for the occurrence of future ventricular arrhythmias.

Supraventricular arrhythmias, especially permanent atrial fibrillation, are rare in children, although episodes of supraventricular tachycardia and atrial fibrillation were recorded in 10% of children with HCM during Holter monitoring.^{49,50} In the rare cases where atrial fibrillation has become established, attempts should be made to restore sinus rhythm and, if this is not feasible, the ventricular response should be controlled with beta-blockers or verapamil. After cardioversion amiodarone is given preventively, while anticoagulation therapy is absolutely indicated in patients who have frequent episodes or persistent atrial fibrillation.

Finally, antibiotic prophylaxis against bacterial endocarditis⁵¹ is indicated in patients with outflow tract obstruction, especially when there is concomitant left atrial dilation (>50 mm).

To conclude, the management of young patients with HCM should initially be focused on identifying those who have an increased risk of sudden death (echocardiogram, Holter, stress test) and applying a prevention strategy (amiodarone or ICD). When there are symptoms these should initially be treated with medication (propranolol or verapamil) and, if that fails, with surgery (Morrow myectomy) when there is a significant degree of obstruction. Intensive exercise and participation in competitive sports must be forbidden, while antibiotic prophylaxis should be given when obstruction is present.

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