Hypertrophic Cardiomyopathy

Cardiomyopathy is defined as a 'myocardial disorder in which heart muscle is structurally and functionally abnormal without coronary artery disease, hypertension, valvular or congenital heart diseases'.[1]

There are five types, namely hypertrophic, dilated, arrhythmogenic, restrictive and unclassified. Cardiomyopathy is a significant cause of sudden death in the young.

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disorder characterised by left ventricular hypertrophy (LVH), impaired diastolic filling, and abnormalities of the mitral valve. These features can cause dynamic obstruction of the left ventricular outflow tract, diastolic dysfunction, myocardial ischaemia, and an increased risk of supraventricular and ventricular tachyarrhythmias.[2]

It is characterised by disorganised cardiac myocytes and unexplained LVH due to mutations in the genes encoding sarcomeric proteins, such as cardiac beta-myosin heavy chain gene, troponin and alpha-tropomyosin.

Adults with increased left ventricular thickness secondary to diseases such as amyloidosis and glycogen storage disease are usually excluded from the definition.

There are separate articles which discuss Cardiomyopathies, Dilated Cardiomyopathies, Arrhythmogenic Right Ventricular Cardiomyopathy and Restrictive Cardiomyopathy.

Epidemiology

- HCM is the most common genetic cardiovascular disease.
- HCM is generally inherited as an autosomal dominant trait with variable penetrance and expressivity.
- A minority of cases reflect a sporadic, non-familial form of the disease.
- The prevalence of HCM is about one in 500 and it tends to affect men and black people more often. The obstructive form is seen in 25% of cases.
- It is also the most common cause of sudden cardiac death in young people and athletes.
- HCM most commonly presents in the second or third decade of life, but may present at any age.
- It is thought that a genetic mutation in one of up to twelve sarcomeric and non-sarcomeric proteins causes histological myocyte disarray and fibrosis in HCM.[2]
- Hypertrophy can occur in any part of the left ventricle, although it is most common in the anterior ventricular septum.
- Troponin T mutations have an increased risk of sudden death, which can occur without evidence of significant LVH.

Presentation

- Most people with HCM are asymptomatic.
- Symptoms may develop at any age.
- The presentation is variable and includes dyspnoea (the most common presenting symptom), chest pain, palpitations and syncope.
- The presentation may be incidental on an abnormal ECG or clinical examination.
- The severity may vary between few or no symptoms and profound exercise limitation, recurrent arrhythmias or sudden death.
- Sudden death is due to arrhythmias and/or obstruction of the left ventricular outflow tract.
- Alcohol ingestion can cause dyspnoea or syncope.
- Unexplained syncope is a risk marker for sudden death.
**Examination**

- Classic examination findings are a forceful apex beat, with double impulse if the left ventricular outflow tract is obstructed and a late ejection systolic murmur, which can be augmented by standing or Valsalva manoeuvre and diminished by squatting.\(^2\)
- Examination may be normal. Abnormal clinical findings include:
  - Left ventricular outflow tract obstruction, which may cause a rapid upstroke and a rapid downstroke in the arterial pulse.
  - The JVP 'a' wave may be prominent due to reduced right ventricular compliance.
  - Outflow tract obstruction may cause a systolic murmur at the left sternal edge, radiating to the aortic and mitral areas.
  - Most patients with left ventricular outflow tract murmurs also have mitral regurgitation.
  - Some patients have an abnormal blood pressure response during upright exercise and systolic blood pressure fails to rise by more than 20-25 mm Hg from baseline values, or falls.
- Atrial fibrillation is the most common sustained arrhythmia in hypertrophic cardiomyopathy, occurring in about 20% of patients, four times the proportion expected in the general population\(^3\).

**Differential diagnosis**

**Other causes of LVH**

- Infants and young children:
  - Most cases are associated with congenital malformations and syndromes, inherited metabolic disorders and neuromuscular diseases.
  - Familial HCM is less frequent in children than in adults.
  - Autosomal dominant disorders that present in the young with LVH include Noonan's syndrome.
  - Occasionally, some children and adolescents present with LVH several years before the development of the neurological and endocrine features of Friedreich's ataxia.

- Adults and adolescents:
  - Most adolescents and adults with HCM have familial disease with an autosomal dominant pattern of inheritance.
  - Some adult patients have non-sarcomeric diseases - eg, Anderson-Fabry disease, mitochondrial disease.
  - Other causes of LVH include obesity, athletic training, amyloidosis and phaeochromocytoma.

**Investigations**

- Electrocardiogram (ECG): most patients have an abnormal ECG, although electrocardiographic features are nonspecific and include LVH, ST segment changes and T-wave inversion.
- Electrocardiographic findings do not correlate with clinical outcome.
- ECG:
  - Findings also may include right or left axis deviation, conduction abnormalities, sinus bradycardia with ectopic atrial rhythm and atrial enlargement.
  - Voltage criteria for LVH alone are nonspecific and are often seen in normal young adults.
  - The most common arrhythmias are premature ventricular complexes, non-sustained ventricular tachycardia and supraventricular tachyarrhythmias.
  - Paroxysmal or chronic atrial fibrillation develops in about 20% of adult patients and is associated with an increased risk of death due to heart failure.
- Ambulatory ECG: findings often include atrial and ventricular ectopy, sinus pauses, wandering atrial pacemaker, intermittent or variable atrioventricular block, and nonsustained atrial and/or ventricular arrhythmias.
- The echocardiogram features of HCM may include:
  - A transthoracic echocardiogram is diagnostic, showing asymmetric septal hypertrophy (usually >15 mm) with a ratio of septal wall to posterior wall thickness >1.4:1.
  - Most patients have a disproportionate increase in the thickness of the interventricular septum.
  - A non-dilated left ventricular cavity.
  - Preserved systolic function.
  - Obstruction of the right ventricular outflow tract is rare.
  - Absence of other cardiovascular diseases capable of producing a similar degree of hypertrophy.
- CXR: findings are variable:
  - Heart size may range from normal to markedly increased.
  - Left atrial enlargement is often seen, especially when significant mitral regurgitation is present.
Cardiac MRI:
- Can measure the severity and distribution of LVH, and provide information on systolic and diastolic ventricular function.
- Can also assess myocardial tissue characteristics and so delineate myocardial infarction in patients with coronary artery disease.
- It is often superior to echocardiography for HCM diagnosis, by identifying areas of segmental hypertrophy (ie anterolateral wall or apex) not reliably visualised by echocardiography (or underestimated in terms of extent). [4]

Cardiac catheterisation: this may be useful to determine the degree of outflow obstruction, diastolic characteristics of the left ventricle, and the anatomy of the ventricles and coronary arteries.
- Exercise testing with simultaneous respiratory gas analysis may be used to assess disease severity.
- B-type natriuretic peptide assays have limited value in hypertrophic cardiomyopathy for prediction of heart-failure symptoms or outcome. [4]
- Endomyocardial biopsy may be required to exclude other causes of increased wall thickness - eg, amyloid.
- Screening for metabolic causes of unexplained hypertrophy is appropriate for affected infants and children.
- Genetic mutations can be identified in approximately 60% of patients; these are most common in genes that encode proteins of the cardiac sarcomere. [5]

Management
- The pathophysiology of HCM is complex, leading to significant variability in clinical presentation. This, combined with the lack of randomised trials, makes the management of these patients difficult. [6]
- The objectives in the management of HCM are to alleviate symptoms and prevent complications.
- A rhythm control strategy with anti-arrhythmic drugs or catheter ablation is often necessary.
- Beta-blockers, verapamil and disopyramide reduce left ventricular outflow tract gradient and diastolic dysfunction, but do not significantly suppress ventricular arrhythmias.
- Amiodarone suppresses atrial and ventricular arrhythmias.
- Atrial fibrillation is common in patients with HCM and is associated with high thromboembolic risk. [7] These patients therefore need to be anticoagulated.
- Radiofrequency catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy is a therapeutic option in patients with drug-refractory symptomatic atrial fibrillation. [3]
- Patients with drug-refractory symptoms or elevated resting outflow gradients qualify for surgical myectomy (primary treatment option) or alcohol septal ablation to reduce left ventricular outflow gradient.
- Patients with multiple risk factors for sudden death benefit from implantable cardioverter defibrillator (ICD) implantation for primary prevention.
- Septal myectomy is an excellent treatment option for those intolerant of or unresponsive to medical therapy. [8]
- Surgical myectomy (or, alternatively, alcohol septal ablation) may be considered for relief of outflow obstruction and symptoms of heart failure. [3]
- Heart transplantation may be necessary in patients with refractory heart failure.
Risk stratification and prevention of sudden death

- Sudden death is the most common cause of death in HCM and occurs more often in young asymptomatic or only mildly symptomatic patients.
- Features such as a history of ventricular fibrillation or sustained ventricular tachycardia, recent unexplained syncope, non-sustained ventricular tachycardia, massive maximal LVH and abnormal blood pressure response to exercise convey a greater risk of sudden cardiac death. [9]
- Age <30 years and a family history of sudden premature death are risk factors for sudden cardiac death in HCM patients. [10]
- ICDs are effective in preventing sudden death in people with HCM. [11]
- Patients who have survived a cardiac arrest or have experienced one or more episodes of sustained ventricular tachycardia are considered at high risk and therefore as candidates for a cardioverter defibrillator for secondary prevention of sudden death.
- Although risk stratification is useful to guide management, such as the option of ICDs for primary or secondary prevention, current methods of risk stratification have limitations. [9]
- A considerable proportion of people who die suddenly do not have 'high-risk' features.
- There is therefore more uncertainty in the selection of patients for primary prophylactic insertion of an ICD.
- Patients with mild LVH (wall thickness <20 mm) and no risk factor can be considered at low risk and have a mean life expectancy similar to that of the general population.
- The risk of infective endocarditis is low and routine antibiotic prophylaxis is no longer recommended. [12]

Genetic counselling

- The number of possible mutations means that genetic testing is not generally practical.
- Careful pedigree analysis of family members can be useful in identifying those at risk of inheriting the disease.
- First-degree relatives of patients with HCM should be regularly screened with ECG and echocardiography.
- The children of affected parents should be screened every three years until puberty, and then every year until they reach the age of 20. If there is no evidence of HCM in their early adulthood, it is unlikely that the condition will develop in later life.

Prognosis

- The clinical course is variable; many remain asymptomatic throughout life but others develop severe heart failure or atrial fibrillation, or die suddenly, often at a young age and in the absence of previous symptoms.
- There may be long periods without any change in the patient’s condition.
- Arrhythmias are common; paroxysmal or chronic atrial fibrillation develops in a minority of adult patients.
- Competitive sports may increase the risk of sudden death.
- Young age at diagnosis, a family history of HCM, and greater wall thickness are associated with a greater likelihood of developing end-stage heart failure. [10]
- Over a period of a few decades, HCM has been transformed from a rare and largely untreatable disorder to a common genetic disease with management strategies that permit realistic aspirations for restored quality of life and advanced longevity. [9]

Further reading & references

- 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy; European Society of Cardiology (Aug 2014)

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