Topic: Hypertrophic Cardiomyopathy

Summary: Hypertrophic cardiomyopathy (HCM) is a relatively common condition affecting the heart muscle and can present at any age. HCM is usually detected by echocardiogram and/or electrocardiogram. Symptoms range from mild shortness of breath on exertion to sudden cardiac death, often in young athletes. Early identification of HCM provides the best opportunity to implement clinical and lifestyle management strategies, potentially reducing mortality. HCM should be considered in cases of sudden death in young people. Since HCM is usually inherited in a dominant manner, at-risk relatives should be referred for cardiac assessment by a specialist familiar with HCM and to a genetics clinic for assessment, counselling, and review of genetic testing opportunities. A growing number of genes are known to be associated with HCM and at-risk testing is available in most provinces. In addition, there are genetic syndromes in which HCM may be a feature (e.g. Noonan syndrome, Fabry disease).

Bottom line: HCM is an important heart condition for which there is growing availability of genetic testing. Any individual with clinical features or family history of HCM should be referred for cardiac and genetics assessment of self, at-risk relatives and genetic testing where indicated.

The Disease:
- Hypertrophic cardiomyopathy
  - A condition in which the myocardium is thickened and the myocytes fibrotic and disorganized, leading to increased risk for heart failure and arrhythmia.
  - Symptoms include dyspnea, chest pain, palpitations, syncope and in some cases, sudden death.
  - Syncope with exercise is a warning symptom of HCM and other potentially heritable heart problems in young athletes and should be thoroughly investigated.1
  - Can present from infancy to the elderly; prevalence: 1/500.2
  - HCM may be isolated or related to a broad spectrum of causes such as inborn errors of metabolism, various syndromes, and neuromuscular disorders. Individuals presenting before the age of 1 year have the most diverse etiologies and poorest outcomes.3
  - Hypertrophy can be septal, apical, or concentric; asymmetrical ventricular hypertrophy is most common.
  - Obstructive HCM occurs when ventricular outflow is compromised.
  - HCM can be associated with sudden cardiac death, even in the absence of marked hypertrophy.
  - Treatment options, dependent on symptoms, include medical management of heart failure & atrial fibrillation, implantable cardioverter defibrillators, surgery, medications that decrease afterload, and avoidance of triggers such as burst activity.
  - Individuals with HCM are usually advised against participation in competitive sport.4
  - HCM can develop secondary to other factors such as longstanding hypertension and significant physical training (athlete’s heart).

The Genes
- Numerous genes are associated with predisposition to isolated HCM. These predominantly include dominantly-inherited genes encoding sarcomeric proteins such as those listed below. Typically, an individual with HCM has a mutation in just one gene; however, some individuals may have two or even three contributing gene mutations.5
  - MYH7 Beta-myosin heavy chain
  - MYBPC3 Myosin-binding protein C
  - TNNT2 Cardiac troponin T
  - TPM1 Alpha-tropomyosin
o TNNI3 Cardiac troponin I
o MYL2 Myosin regulatory light chain
o MYL3 Myosin essential light chain
o ACTC Cardiac actin
o TTN Titin

- Additional genes include 3 systemic conditions, which can present with predominant cardiac features:
  - PRKAG2 AMP-activated protein kinase subunit, associated with HCM and Wolff-Parkinson-White (autosomal dominant).
  - GLA alpha-galactosidase, associated with Fabry disease (X-linked)
  - LAMP2 lysosome-associated membrane protein 2, associated with Danon disease (X-linked)

**Consequences of having a faulty gene**
- A man or woman with dominant HCM due to one contributing gene has a 50% chance of passing the predisposition to HCM to each child.
- Individuals with HCM-associated gene mutations are at risk to develop HCM at any point in life (not just into early adulthood, as previously believed) and should be followed with regular echocardiogram and electrocardiogram surveillance.
- At the present time, genotype-phenotype correlations are not well established (knowing the gene mutation does not predict disease course or response to treatment).

**Testing**
- Most laboratories offering clinical testing for HCM are based outside of Canada.
- Most tests are panel-based, testing multiple genes concurrently.
- Testing can often be arranged via Canadian Genetics Clinics and is most usefully initiated in an individual known to have the disease.
- Test sensitivity for HCM is currently approximately 60%, which means that 40% of individuals tested will not receive an informative result.
- Test results fall into 3 categories:
  - **Positive**: causative gene mutation(s) detected. Diagnosis is confirmed and genetic testing of at-risk relatives becomes available.
  - **Negative**: no causative gene mutation detected. Diagnosis is neither confirmed nor ruled out. There is no genetic test available to determine risk status of relatives.
  - **Variant of unknown significance**: alteration(s) in HCM-related genes are detected, but there is insufficient evidence to determine if they are truly associated with disease. Clinically, these results are usually treated as “negative” and the test is not useful for at-risk relatives.
- All first-degree relatives of an affected person should have regular cardiac exams, echocardiograms & ECGs, unless they test negative for a known familial mutation.

**Who should be offered referral for genetic counselling/testing?**
- Individuals with HCM or with a family history of HCM.

**Benefits of genetic testing**
- Clarification of HCM among individuals with borderline clinical investigations
- Assistance with life planning (e.g., decisions about careers, participation in competitive sports)
- For those who test negative for a known family mutation, relief from worry that they are at greater risk of developing the disease in the future and knowledge that their children are not at risk of inheriting the predisposition to HCM.

**Harms/limitations of genetic testing**
- Adverse psychological reaction, particularly due to potential for risk of sudden cardiac death
- Uncertainty due to a genetic variant of unknown significance

**Review Articles:**


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