Familial Hypertrophic Cardiomyopathy

Praveen Kerala Varma, Narayanan Namboodiri

a. Division of Cardiac surgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India;
b. Division of Cardiology and Electrophysiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India*

ABSTRACT

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Hypertrophic Cardiomyopathy is the most common genetic cardiovascular disease. 70% of affected individuals demonstrate resting or provoked obstruction across the left ventricle (LV) outflow tract. Pathophysiology and clinical course are determined by the hypertrophy of LV. dynamic and mechanical left ventricular outflow tract occlusion, mitral regurgitation, diastolic dysfunction and myocardial ischemia, fibrosis, ventricular tachycardia and risk of sudden death. Patients are initially managed medically, however, significant heart failure symptoms or syncope in spite of optimal drug therapy and significant obstruction require invasive therapy. We report a case of familial hypertrophic cardiomyopathy treated successfully by surgical myectomy.

Keywords: Hypertrophic Cardiomyopathy, Systolic Anterior Motion, Left ventricular outflow obstruction, Heart Failure, Mitral Regurgitation

*See End Note for complete author details

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the commonest genetic cardiovascular disease with a reported prevalence of 1 in 500 persons.[1,2] Majority of cases remain undiagnosed. Many terminologies like Hypertrophic obstructive cardiomyopathy (HOCM), Idiopathic hypertrophic sub-aortic stenosis (IHSS) were used in the past to describe this entity. Increasing awareness, earlier and easy diagnosis by echocardiography and cardiac MRI has led to increased diagnosis and establishment of centers of excellence for comprehensive multimodality management of this complex disease. The disease can present at any age group, however presentation before the second decade of life is very rare. It is one of the most important causes of sudden cardiac death (SCD) in general population.

Genetics: The disease is most often transmitted as autosomal dominant form of inheritance. 14 genes and over 1400 mutations have been identified so far.[3] Sporadic forms are rare. Mutations occur in genes that code for sarcomere proteins. Sarcomeres are the contractile unit of myocardium. Most commonly involved genes are **MYH7, MYBPC3, TNNT2, and TNNI3.** The mutations lead to exuberant hypertrophy of myocardium.

CLINICAL FEATURES

HCM is a heterogeneous disorder with diverse clinical manifestations. Majority of patients achieve normal life expectancy. HCM is defined as non-dilated LV hypertrophy in the absence of other cardiac or systemic causes of LV hypertrophy like hypertension. Clinically in adults, it is diagnosed by the presence of LV wall thickness of > 15 mm by echocardiography or by cardiac magnetic resonance imaging (MRI). 2 different clinical spectrums are identified.[4]

Obstructive form: They account for 70 % of HCM patients. These patients present with obstruction to the left ventricular (LV) outflow tract. Resting or provocative gradients of above 30mm of Hg is present. The obstruction is identified with catheterization or more often by echocardiography with Doppler interrogation. The obstruction has both mechanical and dynamic component. The mechanical component is caused by the asymmetric septal hypertrophy and dynamic component is caused by the systolic anterior motion (SAM) of anterior mitral leaflet **(Figure 1).** Obstructive HCM is often symptomatic and present with syncopal episodes due to decreased cardiac output because of narrowing of LV outflow tract. These are often provoked by exercise. The LV is hypertrophied

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Corresponding Author:
Dr Praveen Kerala Varma, Additional Professor, Senior resident, Division of Cardiac surgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India-695011. E-mail: varmapk@gmail.com

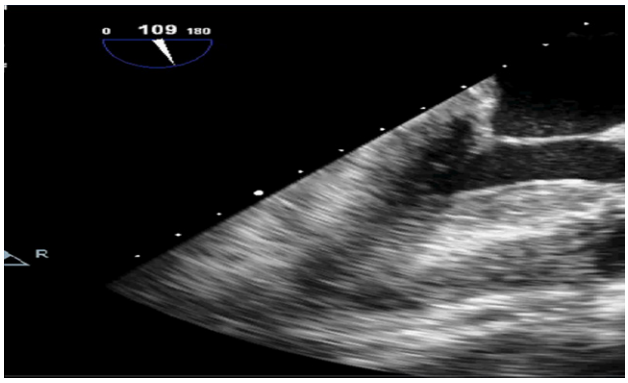

Figure 1. **Echocardiogram- Hypertrophic cardiomyopathy**

Figure Legends: TEE in Long axis view; (Thick arrow) shows the extensive hypertrophy of the Inter ventricular septum. The hypertrophy is typically asymmetrical compared to symmetrical hypertrophy seen in hypertensive patients. Asymmetric hypertrophy denotes hypertrophy of only few segments and typically affects the proximal inter-ventricular septum (arrow).This hypertrophy narrows the LV outflow leading to resting gradients (obstruction). (Thin arrow) shows SAM of mitral valve. The anterior leaflet of mitral valve is bending to the outflow to cause dynamic obstruction. The thickened ventricular septum (shaded area) is resected during surgery to widen the outflow tract (see text for details).

and typically measures more than 15mm in diastole. This hypertrophied ventricle develops diastolic dysfunction, elevated diastolic pressure and secondary elevated left atrial pressure leading to shortness of breath. Demand supply mis-match of the coronary perfusion occurs and can lead to typical angina symptoms. Coronary perfusion anomalies eventually lead to cell death and replacement with collagen. This fibrosis typically starts in the subendocardial region and can extent to a variable degree. Fibrosis acts as nidus for development of ventricular tachycardia and SCD. Fibrosis is identified in Cardiac MRI as late gadolinium enhancement (LGE).[5] Quantification of LGE has important prognostic significance.[5] The dynamic obstruction is provoked conditions that decrease the preload (filling status), or afterload (resistance to the work of ventricle) and increase the contractility or heart rate. Hence these patients poorly tolerate diuretics or ACE inhibitor while drugs decreasing contractility like B-Blockers or calcium channel blockers are used as the first line of therapy. Patients presenting with NYHA Class 3 or 4 symptoms with obstruction demonstrated by echocardiography and on maximal medications are candidates for invasive therapy.[6] Percutaneous alcohol ablation and surgical myectomy are the commonest invasive therapeutic modes. Surgical myectomy remains the gold standard for management of this disease.[6]

Non obstructive forms: Account for 30% of HCM patients. They are managed medically with B-Blockers, small dose of diuretics, Calcium channel Blocker like Verapamil. Patients decompensate with episode of atrial fibrillation. Amiodarone is commonly prescribed in atrial fibrillation. Patients who have documented non sustained ventricular tachycardia are evaluated for Implantable Cardioverter-Defibrillator (ICD). This device can terminate ventricular tachycardia by anti-tachycardia pacing as well as defibrillate ventricular fibrillation, should it occur. In the areas of the world with limited resources, amiodarone is the antiarrhythmic of choice for such patients. Sotolol can be substituted if amiodarone toxicity occurs.

We describe the typical management pattern of a patient who presented with obstructive form of familial HCM.

CASE REPORT

51 year old female without any coronary risk factors presented with history of recurrent palpitations NYHA class 3 for 3 years. She had 4 episodes of syncope and has exertion angina NYHA class 2 and shortness of breath NYHA class 3. Her mother suffered from HCM and had a SCD. Her brother is also diagnosed as HCM. O/E her heart rate was 68/mt regular, BP was 130/80 mm of Hg. Cardiovascular examination showed normal heart sounds with ejection systolic murmur increasing with squatting and Valsalva maneuver. CXR showed no cardiomegaly. ECG was WNL. Transthoracic echocardiography showed ejection fraction of 60 %, asymmetric LV hypertrophy of septum with a peak LV outflow gradient of 45 mm of Hg and associated mid cavity LV gradient of 70 mm of Hg. Holter study showed evidence of paroxysmal atrial tachycardia. She underwent diagnostic coronary angiogram which showed normal coronaries. Hemodynamic study showed peak gradient of 70 mm of Hg which increased to 128 mm of Hg post ectopic beat. LV angiogram showed significant thickening of mid cavity septum with moderate mitral regurgitation. She was put on maximal medical therapy. However on maximal medical therapy she continued to be symptomatic; hence she was referred for surgery.

Intraoperative Trans-esophageal Echocardiography (TEE) examination confirmed the findings of TTE **(Figure 1).** She underwent extended myectomy[7] on cardio-pulmonary bypass (CPB). The surgical steps involve placing the patient on aorto-bicaval cardio pulmonary bypass, aortic cross clamping and arresting the heart with cardioplegia solution. A transverse aortotomy was made to aid the exposure. The aortic valve leaflets were retracted and the thickened inter-ventricular septum was excised beyond the level of mitro-septal contact to the apex of LV. Aortotomy

was closed and after de-airing of the LV, patient was separated from CPB. Post procedure TEE showed a gradient of 6mm of Hg with no SAM and mild mitral regurgitation. She made uneventful recovery. TTE on the 6th post- operative day showed good biventricular function, no gradient across LV outflow tract and mild mitral regurgitation.

DISCUSSION

This case illustrates the classical course of HCM. Her mother and brother were also affected by the disease showing autosomal dominant mode of inheritance. She suffered from syncope attacks denoting obstructive form of disease. Both mechanical and dynamic components were present for LV outflow obstruction. Her ESM increased with Valsalva and by squatting denoting dynamic increase in flow velocity across LV outflow tract. Catheterization showed a resting gradient of 70 mm of Hg which increased to 128 mm of Hg after an ectopic beat. This is because of marked increase in contractility after the induction of ectopic beat. The resultant increase in contractility after extra systole produces an increase in the outflow gradient. Arterial pressure tracing shows more marked spike and dome configuration and exhibit a pulse pressure that fails to increase or actually decreases (Brockenbrough-Braunwald phenomenon). She was placed on maximal medications as the first line of therapy. However she continued to have class 3 symptoms and was referred to surgery following ACC/AHA guidelines.[6] Since she had additional mid cavity obstruction, she was not a suitable candidate for percutaneous alcohol ablation. Alcohol ablation causes necrosis of proximal Inter ventricular septum leading to widening of LV outflow tract. It cannot act on mid inter-ventricular septum. ACC/AHA recommends surgical therapy as the gold standard for HCM and alcohol ablation is offered for patients who are poor surgical risk or do not wish to undergo surgery.[6] Surgery can be accomplished with low mortality and morbidity and offers excellent long term prognosis.[7]

CONCLUSION

HCM is the most common genetic cardiovascular disease. 70% of affected individuals demonstrate resting or provoked obstruction across the LV outflow tract. Pathophysiology and clinical course are determined by the hypertrophy of LV, dynamic and mechanical left ventricular outflow tract occlusion, mitral regurgitation, diastolic dysfunction and myocardial ischemia, fibrosis, ventricular tachycardia and risk of sudden death. Patients are initially managed medically, however, significant heart failure symptoms or syncope in spite of optimal drug therapy and significant obstruction require invasive therapy. Alcohol septal ablation and surgery are the 2 common modes of invasive therapy.

END NOTE

Author Information

1. Dr Praveen Kerala Varma, Additional Professor, Senior resident, Division of Cardiac surgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India-695011.
2. Dr Narayanan Namboodiri, Associate Professor, Division of Cardiology and Electrophysiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India-695011

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