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Case Report

Rare Case of Pediatric Hypertrophic Obstructive Cardiomyopathy (HOCM) in a 6-year-old Boy: How to Recognize, Assess, and Stratify the Risk of Sudden Cardiac Death

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ABSTRACT

Hypertrophic Obstructive Cardiomyopathy (HOCM) is a disease characterized by increased left ventricular (LV) wall thickness and accompanied by obstructive physiology measured by increased LV outflow tract gradient. It is mainly inherited in autosomal dominant traits caused by a mutation in cardiac sarcomere protein genes. In pediatrics, HOCM is rare and comprises a different diagnosis and management approach compared to adults. The risk of sudden cardiac death (SCD) is also higher in the pediatric population. **Case Summary.** This report is about a case of HOCM found incidentally in a 6-year-old boy and a discussion based on the latest literature review. The patient first came for evaluation for cardiac murmur and abnormality in ECG and chest x-ray. Diagnosis of HOCM was made through echocardiography assessment. **Discussion.** ICD implantation for primary prevention of SCD was considered based on individualized 5-year SCD risk assessment which is around 7%. Optimal pharmacological therapy with beta-blocker, careful planning of ICD implantation with balanced benefit and risk, and septal reduction surgery when indicated should extend the life expectancy and quality of life of pediatric HOCM. It is both essential and interesting to recognize pediatric HOCM diagnostic findings and to pursue further research about therapies of this rare disease.

Highlights:

1. It discusses pediatric HCM which is usually caused by autosomal dominant traits caused by mutation in cardiac sarcomere protein genes.
2. It explains how to recognize the cardiac risk.

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Introduction

Hypertrophic Cardiomyopathy (HCM) is a disease characterized by the presence of increased left ventricular (LV) wall thickness, not caused by any abnormal loading conditions[1]. In the United States, the prevalence of unexplained hypertrophy in young adults is expected to be 1:500[2]. Meanwhile, studies about HCM prevalence in Asian populations are rarely available. One Korean population study revealed an escalated HCM prevalence from 0.016 per 100,000 in 2010 to 0.03 in 2016[3]. In the pediatric population, HCM is even less common, with annual cases ranging about 0.3-0.5 per 100.000[1]. National surveillance of rare diseases in Japan revealed in 2015-2019, new cases of HCM in <20-year-old was 0.36 per 100.000[4]. These numbers are expected to be much smaller than the real number, considering many HCM individuals experience no symptoms and do not seek specific medical attention in their life, going undiagnosed. In Indonesia, unfortunately, there is no single official published study that mentions HCM prevalence.

HCM diagnosed in childhood comprises around 14.7% of all HCM. In the first 10 years after being diagnosed, approximately 20% will experience cardiac events with the highest proportion would be life-threatening ventricular arrhythmias, heart failure (HF), sudden death, and atrial fibrillation (AF)[5]. Compared to adults, sudden cardiac death (SCD) in childhood-onset HCM is higher, with a rate of 6.6-9.1% in recent studies[6-8]. Therefore, although considered as a rare disease, pediatric with HCM are highly exposed to increased risk of morbidity and even death as their age is getting older. Thus, it is very important to increase the awareness and the ability to recognize HCM diagnosis earlier especially in pediatric population, and to give optimal management to reduce undesirable outcomes.

In this case report, we aim to refresh and review several latest updates and studies about the assessment, the risk stratification of sudden cardiac death, and management of pediatric HCM through the case presented.

Case Presentation

A 6-year-old boy was referred to outpatient Cardiovascular Policlinic for cardiac murmur and further pediatric echocardiography evaluation. One week prior, he visited a pediatrician for cough and cardiac murmur was discovered upon examination, along with cardiomegaly on chest x-ray. On the day of the cardiovascular policlinic visit, he was accompanied by his grandparents as guardians. His cough had already subsided with medication. When asked about how his daily activities were going, they claimed there was no limitation overall, but indeed they observed he was easier to get tired occasionally. There was no history of growth retardation and speech disorder. History of syncope or palpitations was denied. Another past medical history was also denied. He is the only child of his

parents, his mother died at a young age (30s) of an unknown cause, therefore the boy now lived with the grandparents of his mother.

On vital sign measurement, HR 112 bpm, RR 22x/min, afebrile, SpO2 99% on room air. His height was 110 cm, body weight was 20 kg. Physical examination revealed a systolic murmur. ECG revealed LV hypertrophy with giant R waves and inverted T in both limb and precordial leads (Figure 1).

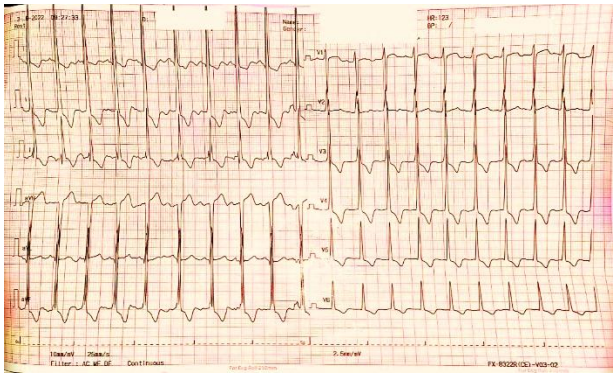


Figure 1. ECG at presentation

Echocardiography was conducted in a rested position. The patient was calm and cooperative. Echocardiography findings were as follows:

- Dimension of heart chamber: LV hypertrophy from basal interventricular septum (IVS) to the apical area with IVS thickness 24 mm, lateral wall thickness 21 mm, apex 20 mm, posterior wall 18.3 mm (Figure 2-3). Normal LA, RA, RV.
- Normal LV systolic function (EF 59%), LV diastolic dysfunction Grade III classified (average E/e' ≥13) (Figure 4), normal RV systolic function (TAPSE 1.6 cm)
- Obstruction on LVOT with pressure gradient 79 mmHg (Figure 5)
- Valves: Mild MR

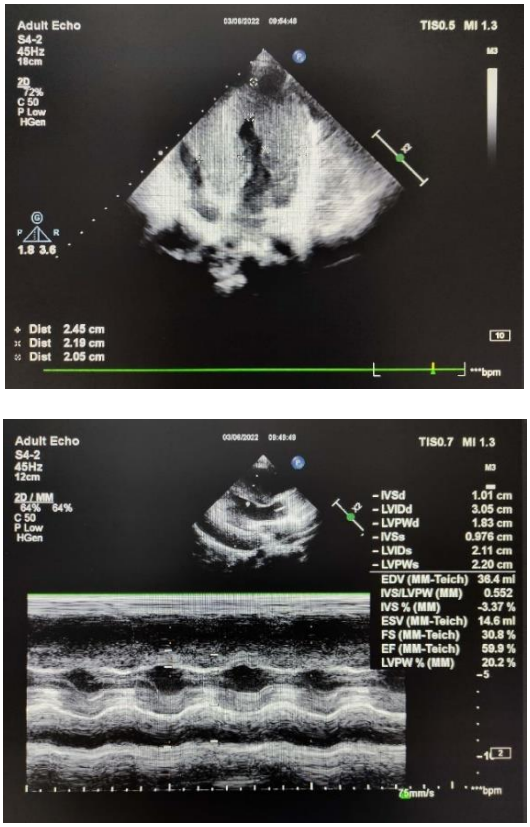
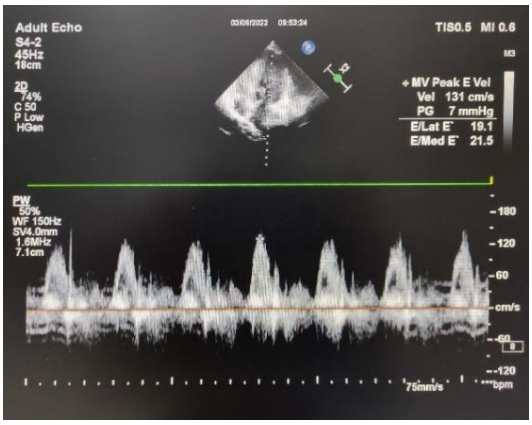


Figure 2-3. Echocardiography show LV hypertrophy: IVS from basal to apical, lateral, and posterior wall with normal LV systolic function EF 59%



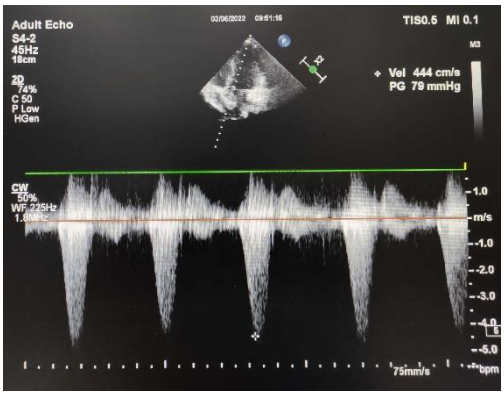


Figure 4-5. (Left) LV diastolic dysfunction with average E/e' ≥13. (Right) LVOT obstruction with gradient 79 mmHg

The patient was assessed with Hypertrophic Obstructive Cardiomyopathy and was prescribed bisoprolol 1 mg once daily. Comprehensive education was given to his grandparents, from the natural course of the disease, restriction in competitive activities or sports, and future risk of life-threatening arrhythmias and sudden cardiac death. They were advised to be referred to pediatric cardiac centers for further evaluation and possible intervention.

Discussion

The majority of HCM is caused by autosomal dominant traits caused by a mutation in cardiac sarcomere protein genes, called primary or sarcomeric HCM. Secondary or non-sarcomeric HCM is caused by other genetic disorders including inherited metabolic and neuromuscular disease, abnormalities in chromosomes, genetic syndromes, and mitochondrial diseases.[1,2,9]

In children, HCM is predominantly (50-60%) caused by sarcomeric compared to a non-sarcomeric cause which globally represents up to 35%, except for the infant (<1 year) population in which non-sarcomeric dominates the cause[5,9]. Those with positive genotype MYH7, MYBPC3, TPM1, and TNNI/TNNT, are the most affected gene, respectively[5,10,11]. Variations of the genotype do not only cause classic HCM phenotype which is myocardial hypertrophy, but also other phenotypes including diastolic function, fibrosis, perfusion dysfunction, and ECG phenotype[12]. These parameters could impact the prognosis of pediatric HCM and thus signaling the importance of genetic testing and family member screening.

Diagnosis

Generally, HCM in children is diagnosed using body surface area-adjusted criteria with increased LV wall thickness z-score >2. AHA recently proposed the new criteria using a higher cut-off, considering the standard z-score >2 represented a significantly lower threshold than adult criteria (15 mm absolute value). AHA recommended using a threshold of z-score >2.5 in asymptomatic children with no family history; whereas z-score >2 in children with a positive family history or genetic testing, for the sake of early screening, detection, and pretest probability of this disease. Wall thickness could be found anywhere in the left ventricle with the basal anterior septum and anterior free wall being the most common location.[2]

By far, the specific z-score threshold has not been yet standardized.

For the presented case, we use the Pediatric Heart Network (PHN) BSA-adjusted echocardiography z-scores models[13]. This patient's IVS wall thickness z-score is 23.4, and LV posterior wall thickness z-score is 16, establishing the diagnosis of HCM.

HCM is then classified into obstructive or non-obstructive. Obstructive HCM is characterized by narrowing of the LV outflow tract[1]. Based on the pattern of septal hypertrophy, LVOT obstruction (LVOTO) is further divided into 2 groups. The first group is subaortic septal hypertrophy resulting from a combination of basal septal thickening, anterior displacement of the mitral valve, and systolic anterior motion (SAM) with or without significant mitral regurgitation from the loss of leaflet coaptation. In this type, systolic pressure is elevated in the entire LV cavity[14,15]. Second group has midventricular obstruction, where the LV cavity is configured like an hourglass. Unlike the subaortic type, systolic pressure at the apical chamber is elevated but normal at the level above the midventricular obstruction[14,15]. Midventricular type can be accompanied by an apical aneurysm or apical pouch which is indicative of progression to end-stage disease with a higher risk of life-threatening arrhythmias and sudden death.[16,17]

Non-obstructive HCM comprises patients without LVOTO, with or without systolic or diastolic dysfunction. Systolic dysfunction often represents the end-stage phase of the disease, resulting from myocardial ischemia, infarction, and myocardial fibrosis[14]. Another subset of non-obstructive HCM present with diastolic dysfunction or a small LV cavity secondary to massive hypertrophy, they often present with severe symptoms. Apical HCM is another variant of non-obstructive HCM characterized by apex myocardial thickening, which developed from subendocardial ischemia related to increased LV wall stress.[15]

Many pediatric HCM patients are asymptomatic, and consultations are mostly for evaluation of cardiac murmur, abnormal ECG and chest x-ray. Another reason is an investigation of cardiac involvement in conditions such as malformation syndrome, an inborn error of metabolism (IEM), or neuromuscular disorders[11,18,19]. In symptomatic patients, fatigue, syncope, palpitations, chest pain, at rest or exertion, and symptoms of heart failure account for most cases[2,20]. SCD as an initial presentation is more common in the pediatric population compared to adults[15]. Clinical history including family history and associated syndromic or organ involvement symptoms should be documented. Assessment of functional capacity and symptoms in response to exertion is important.[2]

Physical findings are frequently related to LVOTO and MR. A blowing systolic murmur is best heard in the left sternal border and apex. The characteristic of

this murmur is the variety of intensity, which intensify or decrease according to the maneuvers that increase or reduces the obstruction. Fourth heart sound related to significant LV hypertrophy may present. While significant obstruction typically causes symptoms in adult HCM, the correlation is unclear in children HCM, probably because children tend to self-limit their activities or have improved compensation at a younger age.[2,15,18]

ECG is usually abnormal in patients and precedes echocardiography findings, even in family members carrying the genotype of probands with HCM. LV hypertrophy with strain pattern is the characteristic finding, another is deep and narrow pathological Q waves and left atrial enlargement (LAE). In younger patients, biventricular hypertrophy, or isolated RV hypertrophy with right axis deviation may present. LBBB may occasionally be present[15,18]. Ambulatory ECG in infants, children, and adolescents revealed that arrhythmias occur rarely in this population. However, after an adolescent period, the occurrence of non-sustained VT is high. Supraventricular tachycardia may be found, atrial fibrillation occurs in the end-stage related to LAE[18]. High rate tachyarrhythmias may lead to syncope and SCD. Based on this regard, ECG could be used for risk assessment of pediatric HCM.[21,22]

Pediatric HCM chest x-ray usually shows cardiomegaly. In more progressive cases, signs of pulmonary venous congestion and pulmonary artery enlargement may present, reflecting elevated LV end-diastolic pressure.[15,18]

Systematic 2D and Doppler echocardiography remain the primary modality for the diagnosis of HCM in pediatric populations. Children tend to have better echo windows compared to adults. Assessment of ventricular morphology, valve function, systolic and diastolic function, and hemodynamics are mandatory. LV hypertrophy is mostly asymmetric, with preferentially IVS involvement than the rest of the walls (lateral, posterior, apex)[15,18]. RV assessment is important to detect any biventricular hypertrophy. Left atrial enlargement is often present because of diastolic dysfunction as well as MR. Doppler allows information about valve function and detection of LVOTO by the pressure gradient.[1,15,18]

LVOTO is defined as peak Doppler LVOT pressure gradient ≥30 mmHg at rest or during provocation such as Valsalva maneuver, standing, and exercise. Gradient ≥50 mmHg is considered where LVOTO becomes hemodynamically important. Asymptomatic patients with LVOTO <50 mmHg should undergo additional exercise stress echocardiography to avoid missed evaluation on resting echocardiography. Unfortunately, provocative maneuvers and exercise tests are useful only in older children, since younger children are often incooperative.[1,2]

Patients with diastolic dysfunction are at higher risk of adverse outcomes, even with preserved EF. Diastolic dysfunction can be assessed using 2 measurements: (1) mitral flow Doppler velocities and (2) tissue Doppler velocities at the mitral annulus level. In children, since mitral flow Doppler velocity is load-dependent, the use of mitral annulus tissue Doppler velocities may be more sensitive in detecting diastolic abnormalities, even in the genetic carriers for early screening before HCM developed.[1,18]

This presented case shows an incidentally found HCM in an asymptomatic patient. This patient was first referred for evaluation of cardiac murmur and cardiomegaly on chest x-ray. ECG clearly shows LV hypertrophy. He falls in NYHA I Classification since he is basically asymptomatic and observed to be easier to get tired just occasionally. On echocardiography, the entire IVS is hypertrophied from basal to apex, but the basal (subaortic) part is prominently bulging along with moderate mitral regurgitation (MR). LVOT pressure gradient is 79 mmHg. These results match with the findings, making the diagnosis of Hypertrophic Obstructive Cardiomyopathy (HOCM) in a 6-year-old child.[2] This case shows that obstructive physiology in HCM may not reflect the symptoms in children, probably caused by a compensatory mechanism in this population[15]. The presence of LV diastolic dysfunction in the obstructive HCM in this patient may highlight the potential adverse outcome and worse prognosis even with preserved EF (59%).

Echocardiography should be done in serial, especially in asymptomatic patients to assess changes in LV wall thickness, systolic and diastolic function, LVOTO, and valvular conditions. Changes in signs and symptoms are often related to disease progression[2,15]. Unfortunately, in this case, the patient didn't show up for scheduled follow up. Echocardiography can also be used to exclude differential diagnosis and appears to be able to predict a tendency of sarcomeric HCM, with reversed septal curvature causing a crescent-shaped LV predicts the gene-positive patient as compared with localized subaortic bulge and preserved septal curvature in non-sarcomeric HCM.[1,15,23]

If available, cardiac magnetic resonance (CMR) is useful especially in patients with an uncertain diagnosis, such as malformation syndrome, suspected metabolic or lysosomal storage disorder, and in children with poor echo windows. Late gadolinium enhancement (LGE) allows detection of the amount of myocardial fibrosis and therefore can be useful in patients with less certain risk stratification since LGE is associated with adverse events in children HCM with decreased EF, degree of heart failure, ventricular arrhythmias, and SCD.[2,24]

Risk Assessment

SCD is the most common cause of death in pediatric HCM and appeared to occur more frequently compared to adult HCM. For a patient with prior events such as aborted cardiac arrest, VF, and sustained VT, implantation of ICD is recommended as a Class I indication for secondary prevention.[1,2] Primary prevention of SCD with ICD for patients who haven't experienced the event, requires risk stratification for ICD insertion consideration.

Previously, pediatric risk stratification was based on adult HCM studies and had limitations in predicting SCD in pediatrics since some items in adult models are considered to differ from the pediatric population. AHA 2020 guideline recommends that the decision for primary prevention with ICD for children HCM should be considered in ≥1 presentation of major risk(s): massive LVH, family history of SCD, unexplained syncope, and NSVT[2]. Left atrial diameter z-scores and resting LVOT gradient are additional considerations since these factors have not yet been used widely in clinical ICD-decision-making studies[2,25]. Reflected to this presented case, massive LVH would fulfill the criteria for consideration of ICD implantation.

On the other hand, several novel pediatric HCM risk stratification models have been developed in recent years, allowing individualized estimation of SCD risk in pediatric HCM[7,8]. The risk items of both models are served in Table 1. These novel risk prediction models emphasize to lead shared decision-making rather than treatment recommendations since ICD implantation in children is associated with higher complications because higher baseline heart rates can lead to inappropriate shocks, infective endocarditis, somatic growth leading to the risk of lead migration and fracture, and the need for multiple device replacements over a lifetime.[2,7,8,26]

Table 1. Novel 5-year SCD risk prediction model

HCM Risk-Kids by Norris et al.[7]	PRIMACY by Miron et al.[8]
Age 1-16 year Prognostic index: • Maximal wall thickness z-score • LA diameter z-score • Unexplained syncope • NSVT • LVOT gradient 5-year SCD risk groups: • <4% risk • 4% - <6% risk	Age <18 year Prognostic index: • Age at first echocardiography • Maximal IVS z-score • Maximal LVPW z-score • LA diameter z-score • Unexplained syncope • NSVT • LVOT gradient 5-year SCD risk groups:

• ≥6% risk (cut off point with 76.5% sensitivity detecting SCD event in 5 years) C-statistic: 0.69	• Low risk: <4.7% • Medium risk: 4.7% - 8.3% • High risk: >8.3% C-statistic: 0.7

In this patient, individualized risk of SCD in 5 years using new risk assessment models, HCM Risk-Kids[7] and PRIMACY[8], resulted in: 7.6% and 6.8% respectively. Taking these into account, ICD implantation should be considered for the primary prevention of SCD in this patient. The benefit, risks, and complications of ICD are highly individualized in each patient, therefore comprehensive discussion between family and a highly competent team is necessary.

Management

Beta-blockers and calcium channel blockers remain the initial medical treatment for both symptomatic and asymptomatic obstructive HCM. Although there is no established evidence that pharmacological therapy can alter hypertrophy, medical therapy aims to reduce catecholamine-induced LVOT obstruction, increased heart rate, and minimize arrhythmia which allows more diastolic filling time.[1,2,15] Beta-blockers are considered the first-line therapy in neonates and children. Verapamil and diltiazem are alternatives because the dominant vasodilating effects of these agents can reduce afterload and may be harmful in patients with very high resting gradients (>80 – 100 mmHg), signs of heart failure, dyspnea at rest, and hypotension. Verapamil may be effective in older infants and children with well-controlled conditions[1,2,15,18]. The target of therapy is improved symptoms and not the measured gradient. Other medications include disopyramide or amiodarone in the presence of an arrhythmia[2]. Agents that may aggravate LVOT obstruction should be avoided, such as dihydropyridine CCB, ACE-I, ARB, and diuretics, although low-dose diuretics may be useful in non-obstructive HCM patients with heart failure symptoms.[2,15]

ICD is the only proven therapy for preventing SCD, thus reducing mortality risk. The decision on ICD implantation in children should be made based on careful considerations of SCD risk, benefits, and complications mentioned in the previous section.[24,25] Unlike in adults, alcohol septal ablation is not indicated in pediatric HCM.[2,15]

Septal reduction with septal myectomy surgery is indicated in patients with resting or provoked gradient >50 mmHg refractory to medical therapy. Surgery may also be advised in asymptomatic or mildly symptomatic (NYHA class II) children with high (75-100 mmHg) or very high gradient (>100 mmHg) at rest, or when there is severe concomitant MR[2,15]. The surgical approach depends on the level of LVOTO: transaortic, midventricular resection, or

transapical myectomy. Surgical myectomy is a challenging procedure especially if it is done in pediatric patients because of their smaller structures, therefore it should be practiced in comprehensive HCM-capable centers[15,28]. One study about septal myectomy in children and young adults reported good survival with 98%, 94%, and 92% at 5, 10, and 20 years, respectively. The mean gradient was reduced from 90 mmHg preoperative to 6 mmHg postoperative[29]. Unfortunately, the authors could not find any Indonesian published study practicing septal myectomy in children or young adults, although alcohol ablation (including percutaneous one) in adult patients had been established more than a decade ago in Indonesian National Heart Center[30,31]. It should be noted that surgical myectomy does not eliminate the need for ICD insertion in high-risk patients.[1,2,15]

In this patient, beta-blocker was given to blunt the sympathetic and reduce catecholamine effects. The family was then advised to be referred to more capable centers for further evaluation and management. Septal reduction with surgical myectomy may be indicated given the high LVOT gradient and concomitant MR. At that time, this patient's family had not consented to the referral plan. Education was given about daily life activities such as avoidance of competitive or timed or graded performance while maintaining moderate daily physical activity. Early screening of the disease for this patient's relatives using echocardiography and genetic testing if available and accessible, should be considered.

Although HCM in children, adolescents, and young adult age groups are considered the population with the greatest risk, low mortality rates can be achieved with optimum management strategies largely relied on ICD implantation in high-risk patients, along with beta-blockade therapy and surgical myectomy for those in indication, giving the opportunity of good quality and extended life expectancy.[32]

This case about pediatric HOCM in a 6-year-old boy gives us some refreshment and the latest updates about the diagnosis, the SCD risk stratification, and the importance of optimal management of this rare disease.

Conclusion

This case is about pediatric HCM incidentally found in a 6-year-old boy with a cardiac murmur, LV hypertrophy in ECG, and cardiomegaly in a chest x-ray. Diagnosis of pediatric HOCM is made by fulfilling the criteria of LV wall thickness BSA-adjusted z-score >2 and LVOT gradient >30 mmHg. In this patient, IVS thickness z-score of 24 and LVPW thickness z-score of 18, along with LVOT gradient of 79 mmHg made the diagnosis. Using two risk assessment models, the 5-year SCD risk in this patient is around 7% and ICD implantation should be considered for primary prevention of SCD with

balanced benefits versus risks. Beta-blocker is indicated in HCM to blunt sympathetic effect. Myectomy surgery may be considered in patients with high gradient and concomitant MR. With optimal medical therapy, SCD prevention, and septal reduction, this patient is expected to have a better life expectancy and quality of life. Little is known about the pedigree history, therefore early screening for relatives should be considered.

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