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MINI-FOCUS ISSUE: HYPERTROPHIC CARDIOMYOPATHY GUIDELINE CASES

INTERMEDIATE

CASE REPORT: CLINICAL CASE

Hypertrophic Cardiomyopathy in Adolescence

Application of Guidelines

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ABSTRACT

We present the course and management of an adolescent male with hypertrophic cardiomyopathy. The importance of family history, early screening, accurate evaluation of hypertrophy, and risk stratification for eligibility for a defibrillator in hypertrophic cardiomyopathy are emphasized. Learning points are seen in the light of new guidelines. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:10–5) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

An 11-year-old male was referred to his pediatrician in 2014 for initial evaluation prior to treatment for attention deficit disorder with stimulant medications. A 12-lead electrocardiography (ECG) performed at that time demonstrated borderline left-axis deviation with nonspecific repolarization abnormalities. There were no voltage criteria for left ventricular (LV) hypertrophy. The physical examination was unremarkable, with no heart murmur and no dysmorphic features or evidence of any systemic or metabolic disorder. The patient commenced methylphenidate therapy without incident. At age 15 years, in 2018, the patient complained of intermittent chest pain during exercise and was referred to his pediatric cardiologist. An ECG performed at that time (**Figure 1**) demonstrated mid-precordial voltage hypertrophy, inferior Q waves, and lateral precordial repolarization abnormalities suggestive of hypertrophic cardiomyopathy (HCM).

LEARNING OBJECTIVES

- To know the diagnostic features of hypertrophic cardiomyopathy in pediatric and adolescent patients.
- To know the indications for defibrillator placement in younger patients with hypertrophic cardiomyopathy.

MEDICAL HISTORY

A family history was obtained, revealing that the patient's father had undergone placement of an implantable cardioverter-defibrillator (ICD) for secondary prevention, following an episode of syncope with associated ventricular tachycardia approximately 10 years prior, at age 50. The father received a diagnosis of HCM at that time, but no further genetic testing or screening had been requested. The patient's paternal grandfather died suddenly at age 49, but the cause was unconfirmed. A family pedigree

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(Figure 2) showed evidence of 3 patrilineal generations of suspected or confirmed familial HCM in the patient's father and uncle and possibly the paternal grandfather. An echocardiogram demonstrated asymmetrical septal hypertrophy with a diastolic septal thickness of 1.6 cm (z-score: 7.5). There was no evidence of LV outflow tract obstruction or any systolic anterior motion of the mitral valve, which was morphologically normal.

DIFFERENTIAL DIAGNOSIS

In the presence of asymmetrical septal hypertrophy at a z-score of >2.5 and with a family history of HCM, a diagnosis of familial HCM was considered most likely. There was no evidence of skeletal myopathy and no features of hepatomegaly or any inherited metabolic disease.

INVESTIGATIONS

The patient then underwent ambulatory ECG monitoring. This revealed minimal ectopy and no exercise-associated ST-segment changes. V_{O_2} (maximum rate of oxygen consumption measured during incremental exercise) and post-exercise stress echocardiography tests were also conducted. The patient achieved a predicted aerobic capacity of 75%, reaching a respiratory exchange ratio of 1.18. No chest pain was evident, and no evidence of any ventricular ectopy occurred. His maximum left ventricular outflow tract systolic gradient was <10 mm Hg immediately after exercise. Cardiac magnetic resonance imaging was not requested. Subsequently, genetic testing in the patient confirmed the presence of a *MYBPC3* mutation. The patient's sibling was offered cascade screening, which was negative. The father was determined to carry the same mutation.

MANAGEMENT

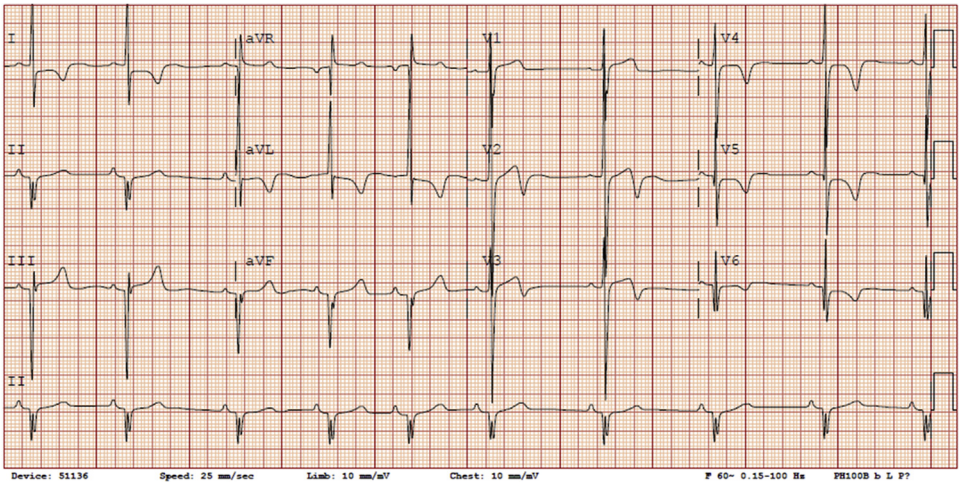
Given his history of intermittent chest pain, the patient was referred to a pediatric electrophysiologist at the authors' institution in 2018. The patient was considered to have insufficient indications at that time for implantation of an ICD. His stimulant medical therapy was continued, and he was started on metoprolol, 25 mg once daily, to address his symptoms of intermittent chest pain. Some restrictions were placed on exercise at that time, and the patient was encouraged to walk or jog but not to participate in competitive high-intensity sports.

In 2019, 12 months later, the patient experienced an episode of syncope after getting out of bed and walking to the bathroom in the morning. The episode was associated with a prodrome of dizziness but no precordial symptoms. There was no retrograde amnesia. A repeated echocardiogram now suggested increased hypertrophy, and the patient was again referred to the authors' care. Of note, the patient had grown approximately 6 cm in height and 14 kg in weight over the previous 12 months.

ABBREVIATIONS AND ACRONYMS

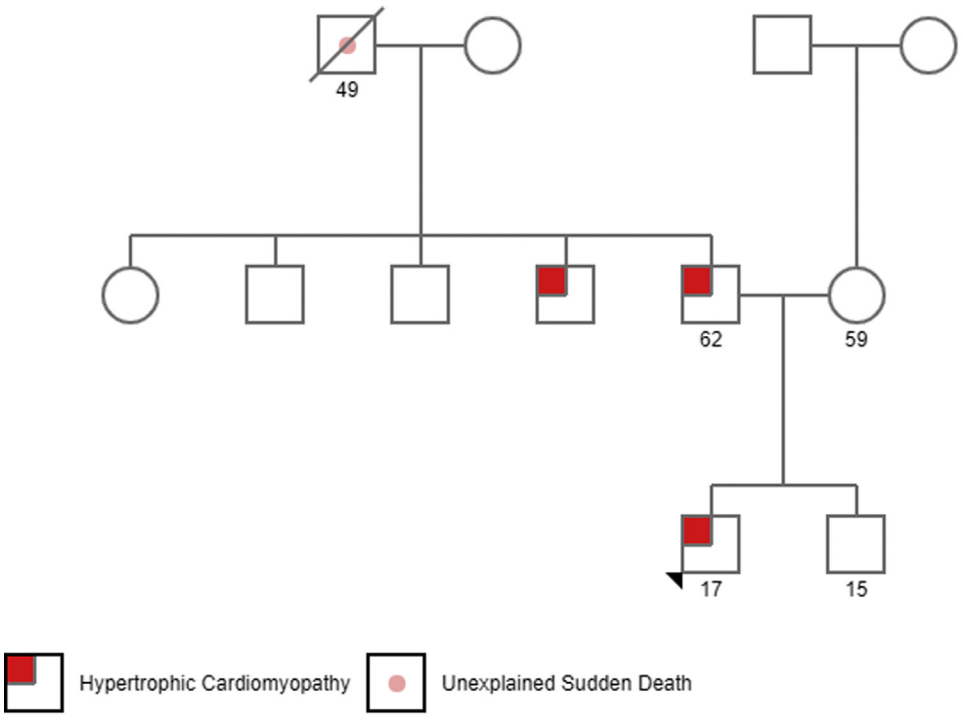
ECG = electrocardiograms
HCM = hypertrophic cardiomyopathy
ICD = implantable cardioverter-defibrillator
LV = left ventricular
VF = ventricular fibrillation
VT = ventricular tachycardia

FIGURE 1 12-Lead Electrocardiogram Performed in This Patient at Age 15 Years at the time of His Assessment by a Pediatric Cardiologist



Note the presence of left axis deviation (−60°), prominent inferior Q waves, prominent mid-precordial voltages, and lateral precordial ST-segment depression and T-wave inversion. All these suggest underlying hypertrophic changes.

FIGURE 2 A Simplified 3-Generation Pedigree Diagram for This Kindred

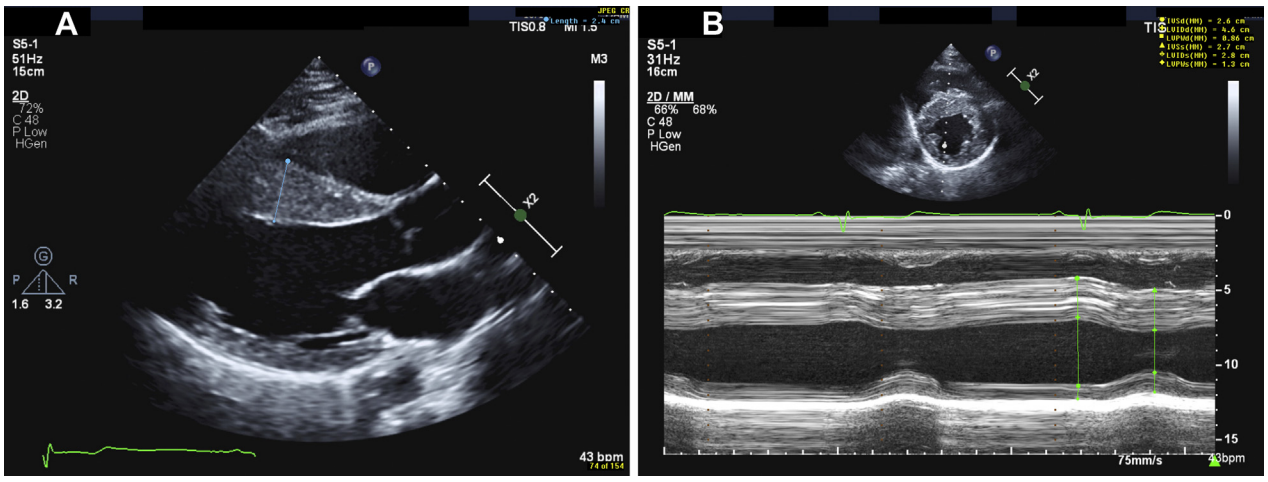


The **arrow** indicates the patient (proband).

Echocardiography now demonstrated a diastolic septal thickness of 2.4 cm (z-score: 13.4) (Figure 3). The syncopal event was judged to be vasovagal in origin. Following discussions with the family and the patient, the authors elected to implant a defibrillator as primary prevention. A transvenous, dual-chamber, single-coil ICD system with antitachycardia capability was selected (Figure 4) and implanted with appropriate defibrillation threshold testing performed at the implantation. The following key considerations for the decision to place an ICD were: the rapid progression of septal thickness and the family history of the patient's father, who had had a life-threatening arrhythmic event.

Nearly 12 months later, in 2020, at 17 years of age, the patient went jogging and had an episode of syncope that required bystander-initiated cardiopulmonary resuscitation. Emergency medical technicians arrived ~15 min later, and the patient's sinus rhythm was noted. He remained unconscious and was intubated at the scene and transported to a tertiary care center. Interrogation of the ICD at the time of the event showed onset of rapid ventricular tachycardia (VT) (to ~240 beats/min). The first burst of antitachycardia pacing from his device resulted in a change to ventricular fibrillation (VF) with intermittent sensing of rapid beats (VT/VF) but no shock for a further 5 min, at which point a 29.4-J shock resulted in conversion to sinus rhythm. Two additional episodes of VF occurred within 1 minute, each ultimately converting to sinus rhythm with subsequent ICD shocks (4 shocks in total for the entire episode). It was concluded that the patient's ICD had not recognized the longer VF due to periods of minimal electrograms (despite maximum sensitivity set at 0.3 mV) (Figure 5), resulting in no shocks delivered for 5 to 6 min. Overall, in 3 of 4 VF episodes (including VF at the time of defibrillation threshold testing at implantation), sensing was appropriate; but with 1 episode, sensing was inadequate. As a result, ICD failure in this case was due to inappropriate sensing as opposed to failed shocks. Echocardiography demonstrated normal systolic LV function with no intracardiac thrombus. The patient made a full neurologic recovery and, following adjustments to the sensing capabilities of his ICD, was discharged

FIGURE 3 **Views of the Left Ventricle and Interventricular Septum**



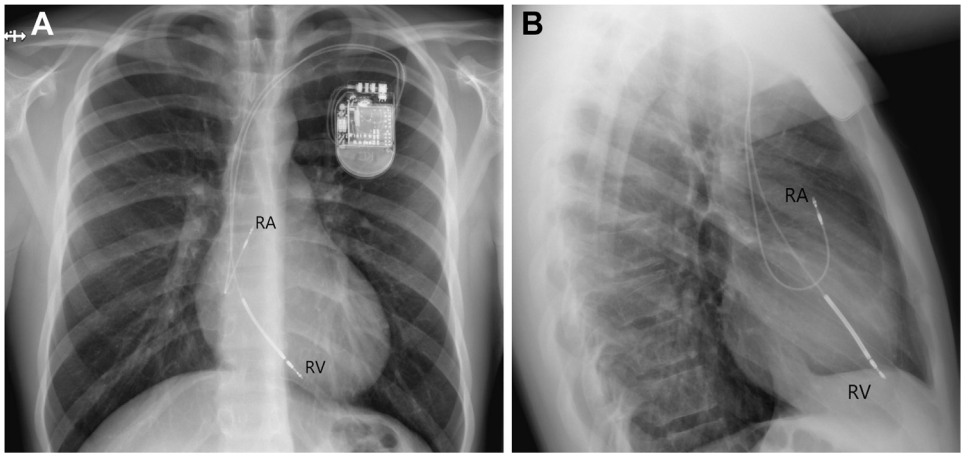
(A) Two-dimensional long-axis echocardiogram view of the left ventricle and interventricular septum, showing hypertrophy, with a morphologically normal mitral valve. **(B)** M-mode in a short-axis view at the midventricular level confirming the presence of asymmetric septal hypertrophy.

with modified medical therapy and tighter restrictions on physical activity. He continued to receive methylphenidate therapy for attentional difficulties as part of a shared plan of care developed with the family. Their expressed priority was to see their son succeed in completing his high school education and to try to reduce impulsive behaviors such as abrupt exercise. The parents felt that the events resulting in his cardiac arrest were partly related to his impulsive behavior and tendency to exercise strenuously without forethought.

DISCUSSION

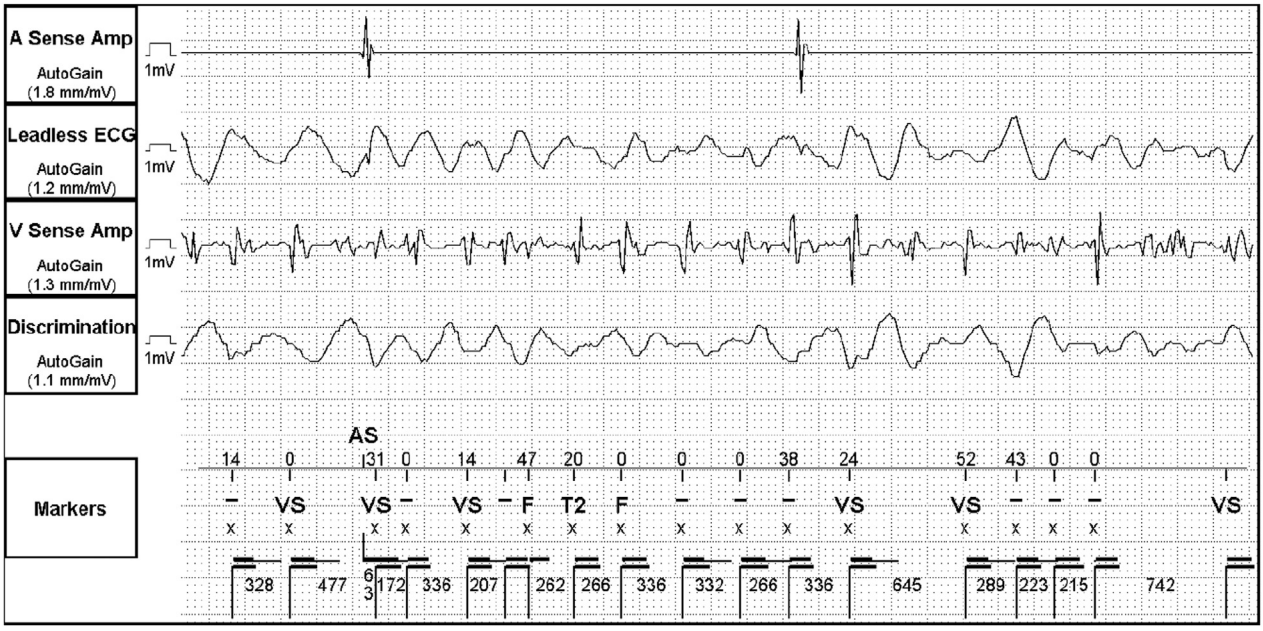
Guideline-based decision making is clearly important at several points in the case history presented. Decisions begin with a detailed family history, which was delayed in this case. It progresses with the

FIGURE 4 **Chest Radiographs**



(A) AP and **(B)** lateral chest radiographs demonstrate the position of the atrial lead at the right atrial (RA) appendage and ventricular implantable cardioverter-defibrillator lead at the right ventricular (RV) apex.

FIGURE 5 Interrogation of the Implantable Cardioverter-Defibrillator



Interrogation of the implantable cardioverter-defibrillator revealed under-sensing of ventricular electrograms during an episode of ventricular fibrillation with relatively small electrical signals seen on the "V Sense Amp" channel.

decision to perform echocardiographic screening, which was also delayed. Both further evaluation of the patient by ambulatory ECG monitoring and exercise testing with post-exercise echocardiography were appropriate, as was referral of the patient for assessment of syncope. All of these measures contributed to assessing his level of risk, culminating in placement of a defibrillator. Because sudden cardiac death remains a common event in young patients with HCM, such risk stratification is a priority, regardless of the age of the patient.

ASSOCIATION WITH CURRENT GUIDELINES. First, current guidelines indicate that a 3-generation family history be obtained to determine whether there is substantial evidence of familial HCM, as was present in this case (Class I recommendation). Second, current guidelines no longer require a lower age limit for ECG and echocardiographic screening of children or siblings of individuals who have either a phenotypic or gene-positive diagnosis of HCM. In the present case, both the patient and his sibling would have been eligible for early screening by ECG, echocardiography, and clinical evaluation at the time of the diagnosis of the father. Definitive echocardiographic diagnosis of HCM in children requires application of z-scores to demonstrate a clear abnormality of LV wall thickness (as was present in this patient). However, the degree of hypertrophy can progress over time, requiring serial surveillance echocardiography. Third, genetic testing has now become widely available and is recommended (Class I recommendation) for the purpose of diagnostic confirmation and cascade testing of family members if desired. Regardless of immediate evidence of the HCM phenotype, gene-positive patients are considered at risk for developing progressive hypertrophy and require ongoing surveillance testing on a 1- to 2-year basis in childhood (Class I recommendation).

Once a diagnosis of phenotypic HCM is established, there is a Class I recommendation for exercise stress testing and ambulatory ECG monitoring, as was obtained in this patient. These tests establish the presence of latent outflow tract obstruction (using stress echocardiography). The use of a beta-adrenergic receptor antagonist is also indicated (Class I recommendation) in situations of nonobstructive HCM with angina pectoris, although the definitive diagnosis of angina in pediatric patients can be challenging.

There remains no Class I recommendation for an ICD for primary prevention of sudden cardiac death in HCM patients (i.e., in the absence of cardiac arrest or documented ventricular tachycardia). Therefore, the

decision to implant an ICD in this patient as a means of primary prevention was based on a shared decision making model and was supported by Class IIa recommendation: as a child with evidence of progressive but not massive hypertrophy and a clear family history of a high-risk arrhythmogenic event, as evident in this patient's father, the decision for defibrillator placement was made with due consideration of the risk of long-term presence of a defibrillator in young patients. Shared decision making is considered essential in this matter, for both adults and children with HCM, on the basis of objective demonstration of risk. Sudden death is more closely linked to a family history of sudden death, the severity of hypertrophy, the presence of prior documented ventricular tachycardia or arrhythmogenic syncope, and evidence of ventricular fibrosis, among other secondary indicators in adults. In this context, risk calculation algorithms for an individual quantification of risk for a cardiac arrhythmia event, the understanding of the risk of such an event, and how this influences the decisions of the patient and family must be incorporated into individualized expert counseling (1,2).

Finally, it is now recommended that exercise restrictions be individualized, with the need to permit most patients with HCM to continue mild to moderate exertion now given a Class I recommendation. In the RESET-HCM (Randomized Exploratory Study of Exercise Training in Hypertrophic Cardiomyopathy) study, a randomized controlled trial showed that exercise training improved aerobic capacity in HCM patients, with no major adverse events associated, and in another pilot study, quality of life was improved by permitting exercise in these patients (3,4).

CONCLUSIONS

This case illustrates the fact that assessment of risk for sudden cardiac death in adolescents with HCM can be a dynamic process and can change over time. The difficulties that occur are unique in adolescents, who are growing rapidly and whose septal thickness dimensions may change as they grow. We note that, although extreme hypertrophy is conventionally interpreted as a septal thickness of 3 cm in adult patients, this threshold dimension does not clearly apply to children or adolescents and that an individualized decision regarding risk for sudden cardiac death often must be developed. Recently published risk assessment tools in children with HCM are useful in this regard (5,6). One of these assessment tools suggests that the risk of sudden arrhythmic events increases with progressive hypertrophy before reaching a plateau, which occurs at a z-score of 22 (6). This score, however, represents a septal thickness of <3 cm in most pediatric patients. Normalization of hypertrophy according to z-scores derived from body surface area is therefore necessary for the diagnosis of HCM in all children and may also be necessary in the assessment of risk for sudden cardiac death. Several important learning points are reinforced by the current guidelines developed by the American College of Cardiology/American Heart Association.

AUTHOR DISCLOSURES

Dr. Kantor serves as a Scientific Advisory Board member for Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cardiomyopathy, ventricular fibrillation, ventricular tachycardia

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