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CASE REPORT

Cardiac Amyloidosis in a Child Presenting with Syncope: The First Reported Case and a Diagnostic Dilemma

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Abstract
Cardiac amyloidosis is a rare cause of cardiomyopathy, reported exclusively in adults. We report the first known case presenting in childhood. A 12-year-old boy presented with syncope and diagnosed with ventricular non-compaction by echocardiography. Eventual genetic testing confirmed a TTR gene mutation associated with hereditary transthyretin amyloidosis.

Keywords Cardiac amyloidosis · Transthyretin amyloidosis · Arrhythmia · Cardiomyopathy

Introduction

Transthyretin (TTR) amyloidosis is a progressive and systemic disease characterized by the extracellular deposition of amyloid fibrils composed of TTR. TTR cardiac amyloidosis is a well described form of cardiomyopathy that has been reported almost exclusively in older adults [1]. We report the first known case of pediatric cardiac amyloidosis associated with a well-known mutation (Val122Ile) of hereditary transthyretin amyloidosis.

Case Presentation

A 12-year-old, active-for-age, African American male was referred following a single syncopal event while walking. Pertinent findings on initial examination showed a heart rate 52/min, BP 115/55 mmHg, 02 saturation 99%, and grade 1/6 systolic murmur. Other than mild autism, he had no known medical conditions, was active in football and basketball, and on no medications. For the prior month he complained of intermittent and non-specific chest pain, fatigue and shortness of breath. Although other family members have asthma, he had never been tested. There were no known familial cardiac conditions but a maternal grandmother had died suddenly at 45 years of age. Initial testing included a 15-lead electrocardiogram (ECG), 24-h Holter monitor and echocardiogram. The ECG showed wandering atrial pacemaker (average 46/min), normal PR, QRS, QTc intervals and no abnormal ST-T wave changes or hypertrophy. Transthoracic echocardiogram revealed normal cardiac relationships with marked left ventricle (LV) trabeculations (Fig. 1). The 24-h Holter monitor showed heart rates ranging from 36 to112/minute (sinus/atrial), 58 single ventricular ectopic complexes (PVCs), no couplets, no ventricular tachycardia.

Based on the initial study results, additional evaluations with cardiac magnetic resonance imaging (MRI) and exercise stress testing were performed. Cardiac MRI revealed the ratio of non-compacted to compacted myocardium > 2:1 from the mid-body to the apex with the LV ejection fraction measuring 52.13% (Fig. 2).

Exercise stress test showed frequent PVCs and non-sustained bidirectional ventricular tachycardia (Fig. 3).

Based on these findings, a clinical diagnosis of cardiac non-compaction was made, Nadolol therapy was initiated and a dual-chamber defibrillator (ICD) was implanted. Familial genetic testing was strongly recommended but not implemented. He continued on Nadolol therapy and remained asymptomatic for the next 6 years with only rare episodes of short, non-sustained atrial and ventricular arrhythmias detected during device interrogation at scheduled clinic visits. His clinical course was otherwise

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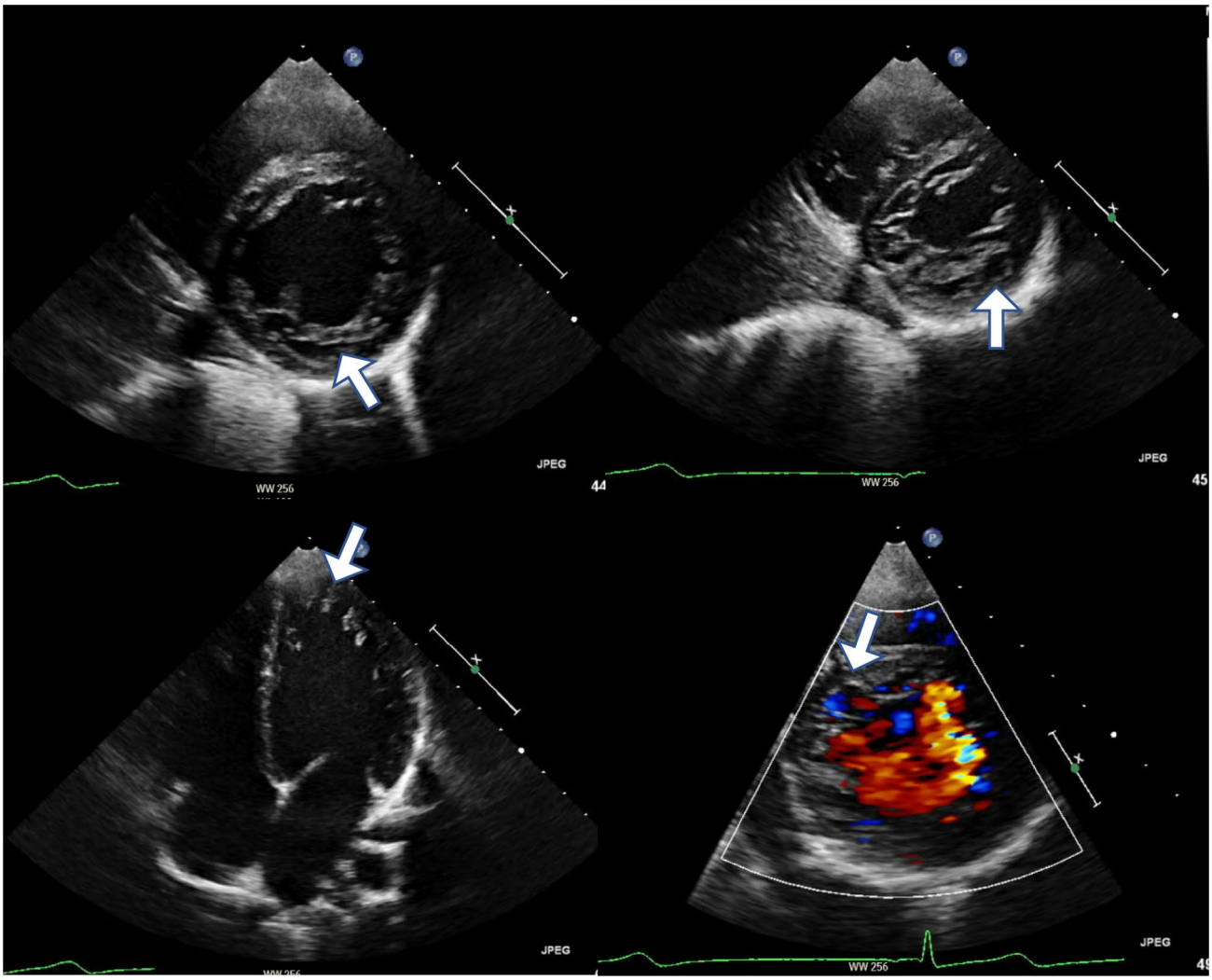

Fig. 1 Transthoracic echocardiogram/Color Doppler in cross sectional and 4 chamber views showing marked trabeculations and spaces (arrows)

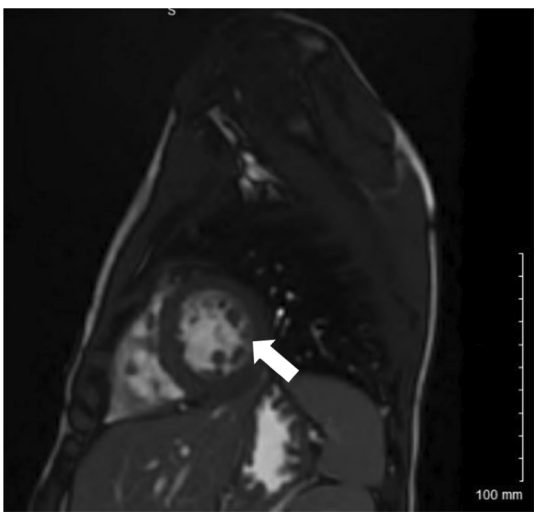

Fig. 2 MRI sagittal view showing areas of abnormal LV trabeculations (arrow)

unremarkable and repeat echocardiograms remained unchanged. At the age of 18 years, he suddenly experienced inappropriate ICD shocks not associated with any arrhythmias. Device interrogation showed inappropriate sensing with an increase in lead impedance. A chest radiograph illustrated lead displacement. He underwent lead extraction with scheduling for a new device implant. Genetic testing was performed during that admission and identified a pathogenic variant in the TTR gene (c.424G > A [p.Val142Ile]) associated with the autosomal dominant heredity transthyretin-mediated amyloidosis. Additional familial genetic testing revealed that his asymptomatic mother and both siblings (18 and 21 years of age) all tested positive for the same pathogenic variant.

He persistently had no symptoms of heart failure and measured BNP and troponin levels were normal. To investigate any burden of disease, additional evaluations including scintigraphy with technetium 99-m pyrophosphate

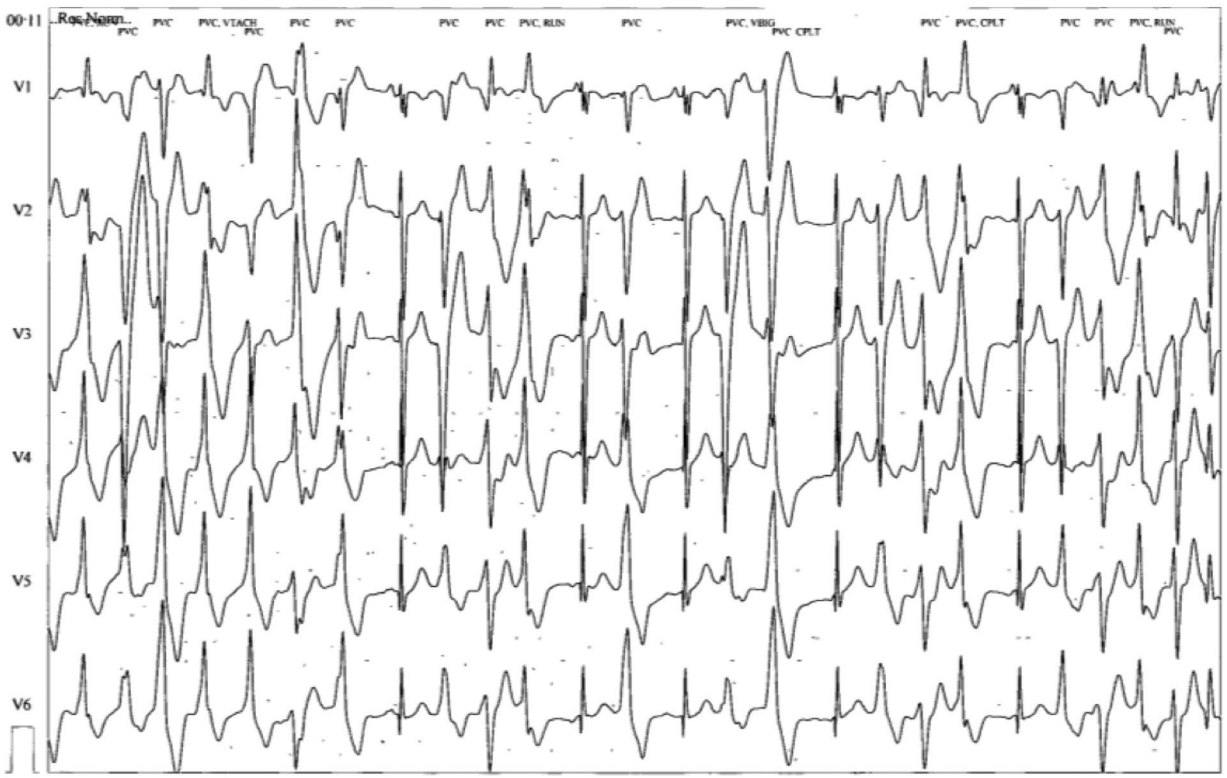

Fig. 3 Exercise stress test. Tracing obtained during exercise test showing bidirectional tachycardia

were performed and revealed no cardiac radiotracer uptake. Serum free light chains, serum and urine electrophoresis with immunofixation were normal without evidence of a monoclonal gammopathy. There was no evidence of cardiac amyloidosis on gadolinium magnetic resonance imaging. A sensory-motor nerve conduction study is planned in the near future to assess for bilateral median nerve involvement. Given that he is a carrier of the pathogenic variant Val-142Ile, close monitoring is continuing. At present, there are no indications for any additional treatment (e.g., Tafamidis).

Discussion

Transthyretin (TTR) amyloidosis is a progressive and systemic disease characterized by the extracellular deposition of amyloid fibrils throughout the body. When cardiac involvement occurs (transthyretin amyloid cardiomyopathy [ATTR-CM]), deposition and infiltration of fibrils occurs and cause stiffness with ventricular dysfunction, leading to progressive heart failure with a poor prognosis [1]. There are three clinical forms of ATTR-CM: acquired monoclonal immunoglobulin light chain amyloidosis (AL-CM), wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM) with no mutation identified, and hereditary transthyretin amyloid CM (hATTR- CM) [2]. This hereditary or familial form has been linked with more than 120 pathogenic mutations in the TTR gene, resulting in variable phenotypes. The most common gene mutation described in the United States associated with hATTR-CM is the Val122Il mutation, which is transmitted in an autosomal dominant manner with variable penetrance. This mutation manifests predominantly as a cardiomyopathy, and has been identified in 3.5% of the African American population. Likewise, 10% of older (> 60 years) African Americans with heart failure are carriers of the Val122Il mutation [3]. The clinical course of ATTR-CM is variable and includes symptoms of progressive heart failure as well as findings of altered QRS morphologies on ECG, atrioventricular block, sinoatrial dysfunction and/or atrial and ventricular arrhythmias. The disease progression and life expectancy of ATTR-CM is worse for individuals with the hATTR (caused by Val122Ile mutation) compared to the wtATTR variant [4].

As evident in this case, the diagnosis of cardiac amyloidosis is challenging since echocardiographic findings can be similar to more readily-identified forms of cardiomyopathy seen in childhood such as hypertrophic cardiomyopathy (HCM) and LV non-compaction (LVNC). All can have abnormal myocardial thickness and/or prominent trabeculations with deep recesses [5, 6]. Due to this

diagnostic dilemma, initial evaluations should include cardiac echocardiograms, MRI and myocardial scintigraphy. Endomyocardial biopsy can still be advised in instances where non-invasive findings are inconclusive or in the presence of a monoclonal gammopathy, due to its almost 100% sensitivity and specificity for detecting amyloid deposits. In the current era, genetic testing is indispensable and should always be performed in all patients with any cardiomyopathy, to assure appropriate drug therapy as well as provide appropriate genetic counseling.

ATTR-CM has been previously reported as an underrecognized cause of heart failure in older adults and its true prevalence has probably been underestimated. To our knowledge, it has never been reported in childhood. Our patient has the cardiac genotype as confirmed by genetic testing. It is anticipated that disease penetrance will be more manifest with age [7]. Accordingly, he will be evaluated every 3–5 years to determine when to initiate Tafamidis therapy [8].

Conclusions

Transthyretin amyloid cardiomyopathy is a rare cause of arrhythmias and heart failure with a poor prognosis that has never been previously described in childhood. Genetic testing should always be performed in any patient, of any age, with an apparent cardiomyopathy regardless of seemingly diagnostic non-invasive testing.

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Declarations

Conflict of interest The authors have no conflicts of interest relevant to this article to disclose.

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