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Hypertrophic cardiomyopathy in Duchenne muscular dystrophy: a case series

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Brief Report

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Abstract

Duchenne muscular dystrophy is characterised by fibrofatty replacement of muscle, resulting in dilated cardiomyopathy. Hypertrophic cardiomyopathy affects 1:200–1:500 people and is characterised by asymmetric ventricular septal hypertrophy. To date, there have been two separately reported cases describing the combined pathology of these disorders. Herein, we expand upon these reports with a case series describing longitudinal findings in three patients with Duchenne muscular dystrophy who developed hypertrophic cardiomyopathy.

Introduction

Patient A

Patient A is a 16-year-old diagnosed with Duchenne muscular dystrophy at 3.5 years old in the setting of gross motor delays. He was started on daily corticosteroids (prednisone) at the time of diagnosis. At age 10, he developed late gadolinium enhancement in a typical Duchenne muscular dystrophy pattern and was prescribed spironolactone. He had normal biventricular size and systolic function. At age 12, an echocardiogram demonstrated new asymmetric septal hypertrophy with a left ventricular outflow tract peak gradient of 19 mmHg, systolic anterior motion of the mitral valve, and mild mitral regurgitation. His blood pressure was normal on multiple measurements. Subsequent MRI showed mid- and basal inferoseptal hypertrophy. These findings prompted genetic testing (Inviate HCM gene panel), which revealed a *de novo* pathologic variant in the *MYBPC3* gene.

The patient's current cardiac findings include a septal dimension of 1.5 cm at end-diastole (Figure 1a) with low-normal systolic function and progression of late gadolinium enhancement with septal sparing (Table 1). Over time, he has been maintained on spironolactone and metoprolol succinate. Angiotensin-converting enzyme inhibitors have been deferred due to his hypertrophy and outflow tract obstruction. He is now 17 years old, continues to ambulate short distances, and has no history of arrhythmia.

Patient B

Patient B is a 31-year-old diagnosed with Duchenne muscular dystrophy at age 4 in the setting of weakness and calf hypertrophy. He started daily corticosteroids (deflazacort) at age 8 with loss of ambulation at 19.5 years. He developed asymmetric septal hypertrophy on MRI at age 23. He had no systolic anterior motion of the mitral valve, mitral regurgitation, left ventricular outflow tract obstruction, or late gadolinium enhancement at the time. His blood pressure and biventricular function were normal. He subsequently underwent HCM-specific genetic testing which resulted in a variant of uncertain significance in *TNNT2*.

Since his clinical diagnosis, he has developed progressive hypertrophy with a maximum septal dimension of 1.5 cm at end-diastole (Figure 1b) with patchy late gadolinium enhancement. On his most recent echocardiogram, he was found to have a left ventricular outflow tract peak gradient of ~50 mmHg with systolic anterior motion of the mitral valve and mild mitral regurgitation. His biventricular function remains normal. He has a history of non-sustained ventricular tachycardia on Holter monitoring at age 29 (Table 1). The family has deferred implantable cardioverter defibrillator given his relatively low arrhythmia burden and the anaesthesia considerations. From a medication perspective, he was on prophylactic lisinopril and carvedilol for a history of sinus tachycardia. The family elected to continue with each drug class over time, although the carvedilol was transitioned to metoprolol succinate given his left ventricular outflow tract obstruction. Spironolactone was added at age 30 after development of late gadolinium enhancement. The patient is currently 32 years old and doing well.

Patient C

Patient C was diagnosed with Duchenne muscular dystrophy at age 4 in the setting of gross motor difficulties. He was started on daily corticosteroids (deflazacort) at diagnosis and

Table 1. Patient data

	Dystrophin variant	Age at clinical HCM diagnosis	Genetic variant (HCM)	Arrhythmia history	Maximum septal thickness on MRI (end-diastole)	Most recent LVEF	Most recent LGE burden
Patient A	Duplication of exons 56-63 (frameshift)	12	*De novo* pathologic variant in *MYBPC3 (c.2510_2513del [p. Ile837Argfs*41]).*	None by symptoms or ambulatory testing	1.5 cm (mid- and basal inferoseptal segment)	53%	Subepicardial and mid-myocardial changes in the mid and basal portions of the infero- and anterolateral segments
Patient B	Nonsense mutation of exons 46-47 (out of frame deletion)	23	Variant of uncertain significance in *TNNT2*	One episode of NSVT (11 beats at 136 beats per minute)	1.5 cm (mid-anteroseptal segment)	62%	Patchy involvement of the anteroseptal segment
Patient C	Deletion of exons 5-13 (frameshift)	14	Variant of uncertain significance in the *MYL2 gene (c.49G>A (p. Val17Met)*	None by symptoms or ambulatory testing	1.5 cm (basal anteroseptal segment)	55%	Subepicardial and transmural changes in the lateral, mid-ventricular, and inferolateral segments

HCM = Hypertrophic Cardiomyopathy; LVEF = Left Ventricular Ejection Fraction; LGE = Late Gadolinium Enhancement; NSVT = Non-Sustained Ventricular Tachycardia.

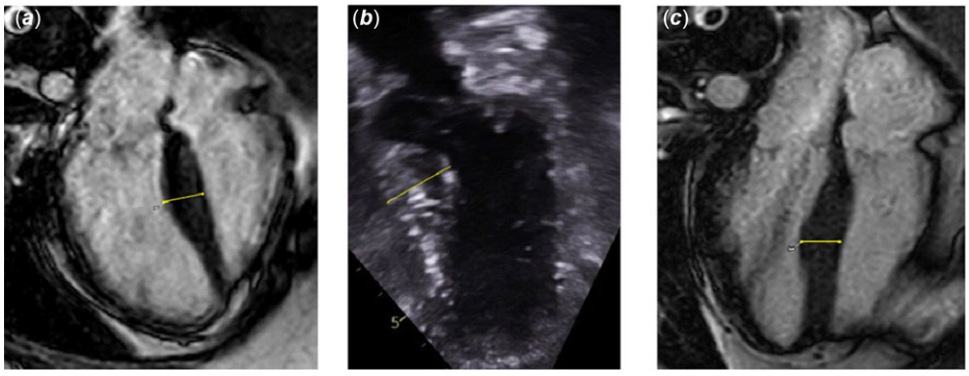

Figure 1. a) Patient A. CMR at age 16 Maximal septal dimension of 1.5 cm. (b) Patient B. Echo at age 31 Maximal septal dimension 1.5 cm with an LVOT of 50 mmHg. (c)Patient C. CMR at age 19 Maximal septal dimension of 1.5 cm.

experienced loss of ambulation at 14.5 years of life. He developed late gadolinium enhancement in a typical distribution on MRI at age 10 and was started on lisinopril. At age 14, he developed asymmetric septal hypertrophy with maximal end-diastolic dimension of 1.29 cm (*Z*-score 3.3). He underwent HCM-specific genetic testing, which revealed a variant of uncertain significance in *MYL2*. The patient's lisinopril was stopped as the risks were thought to outweigh the benefits given his newly diagnosed septal hypertrophy and no history of cardiac dysfunction. He was started on spironolactone at age 15 given development of late gadolinium enhancement, and metoprolol succinate at age 16 in the setting of hypertrophy and resting tachycardia. Lisinopril was restarted at age 17 due to progression of late gadolinium enhancement and new onset systolic dysfunction (left ventricular ejection fraction 50%). His systolic blood pressure remained largely age appropriate before and after initiation of these medications.

Over time, he had mild progression of his septal hypertrophy (maximum septal dimension 1.5 cm at end-diastole) but never developed left ventricular outflow tract obstruction or systolic anterior motion of the mitral valve (Figure 1c). He did have progression of late gadolinium enhancement (Table 1), but none in the areas of hypertrophy. He had normalisation of his cardiac function following re-initiation of lisinopril in his late teens. At age 20 he developed fever, cough and dyspnoea. Following intubation, he developed a large tension pneumothorax with hemodynamic compromise and death.

Discussion

Herein, we present a case series with follow-up of patients with Duchenne muscular dystrophy who developed features consistent with hypertrophic cardiomyopathy. One patient had genetic testing confirming a pathologic variant while the others had variants of uncertain significance in genes suspicious for involvement in hypertrophic cardiomyopathy on an Invitae HCM-specific genetic panel testing 26 specific genes known to be involved in HCM. None of the patients had a family history of cardiomyopathy or muscular dystrophy.

In Duchenne muscular dystrophy, the average age of onset for systolic dysfunction is ~15.2 years with rate of decline ~1–2% thereafter.[1] In hypertrophic cardiomyopathy, ventricular function is characteristically normal.[2] While all patients included in this series were older than 15 and had evidence of late gadolinium enhancement, ventricular systolic function was generally preserved (low-normal in patient A and transient, mild dysfunction in

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patient C). Similarly, the two previously published case reports describing similar dual-phenotype patients report normal or hyper-dynamic function in their patients (age 27 and 16 respectively).[3,4]

Given function has been preserved, there was also appreciable concern for atrial and ventricular arrhythmias, which can occur in both hypertrophic cardiomyopathy and Duchenne muscular dystrophy.[5,6] Regarding medical treatment, we have focused on a patient-guided approach especially for angiotensin-converting enzyme inhibitors. This class of medication is often used in the treatment of Duchenne muscular dystrophy but is generally contraindicated in patients with hypertrophic obstructive cardiomyopathy who have normal systolic function.[7] Our conversations have focused on the overall dystrophinopathy phenotype and severity of involvement given the lack of data regarding the optimal long-term approach. Similarly, the discussion regarding defibrillator placement in patient B, who has a class 2b indication for an implantable cardioverter defibrillator based on his history of non-sustained ventricular tachycardia and late gadolinium enhancement[7] has focused on balancing the risk of sudden death in hypertrophic cardiomyopathy with the patient's dystrophinopathy phenotype and comorbidities.

Duchenne muscular dystrophy and hypertrophic cardiomyopathy are rare co-occurring disorders with varying clinical phenotypes requiring sometimes divergent clinical practices (e.g. use of afterload reducing agents). Given the population frequency of these conditions, individual cases will be rare, but not extremely so, given 1:500 people have hypertrophic cardiomyopathy.[8,9] Our clinical experience suggests it is reasonable to take a considered approach to therapy as the coexistence of these diseases does not dictate a uniformly worse prognosis.

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Competing interests. None.

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