CLINICAL VIGNETTE

Cardiomyopathy Complicated by Cardiogenic Shock Secondary to Limb-Girdle Muscular Dystrophy

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Introduction

Limb-girdle muscular dystrophy (LGMD) included a broad array of inherited muscular dystrophies, often associated with cardiomyopathy and conduction disease, even in the absence of marked neurologic deficits. Our patient presented with new-onset severe cardiomyopathy and cardiogenic shock and was ultimately diagnosed with LGMD type 2I after extensive evaluation.

Case

A 28-year-old high-functioning autistic man presented to an outside hospital with dyspnea, intractable nausea/vomiting, lower extremity edema, and weakness which had progressively worsened over two months. He had no known medical problems other than his autism. He was initially mildly hypotensive to as low as 100/76 mmHg and was given approximately five liters of intravenous fluids over two hospital days for possible hypovolemia in the setting of poor oral intake and emesis. He subsequently developed severe respiratory distress with crackles bilaterally, elevated JVP, and worsening hypotension, requiring emergent intubation. His labs were significant for a BNP of 1900, along with ALT of 348 u/L and AST of 368 u/L. Transthoracic echocardiogram demonstrated a severely dilated left ventricle (left ventricular end-diastolic dimension of 7.0 cm) with severe biventricular systolic dysfunction and a left ventricular ejection fraction (LVEF) of 10-15%. He had worsening hypotension as low as 73/54 mmHg, consistent with cardiogenic shock. He was initiated on norepinephrine, dobutamine, and dopamine for hemodynamic support and an intra-aortic balloon pump (IABP) was placed. He was emergently transferred to our hospital for higher level of care.

Upon arrival, he remained critically ill and hemodynamically unstable. A pulmonary artery catheter was placed for hemodynamic monitoring. Right heart catheterization revealed a right atrial pressure of 8 mmHg, pulmonary artery pressure of 51/30 mmHg (mean 39 mmHg), pulmonary capillary wedge pressure (PCWP) of 25 mmHg, cardiac index of 1.69 L/min/m2, and systemic vascular resistance of 1668 dynes-sec/cm5, consistent with cardiogenic shock. Emergent evaluation was initiated for possible heart transplantation or left ventricular assist device (LVAD). However, with aggressive diuresis and mechanical support, his condition improved. He was responsive to intravenous boluses of furosemide. The IABP was removed the following day and the patient was extubated. The inotropes were slowly weaned off and he was slowly initiated on optimal medical therapy, including enalapril, metoprolol, spironolactone, and torsemide as tolerated by his blood pressure. His LVEF remained low, and he had recurrent runs of non-sustained ventricular tachycardia on a near daily basis. He was considered high risk for sudden cardiac death given his high diuretic requirements and his LVEF was unlikely to recover given the large ventricular size. In addition, his compliance with a wearable defibrillator was a potential concern given his autism. After multidisciplinary discussion with our electrophysiology and advanced cardiomyopathy services, a single-chamber ICD was implanted for primary prevention of sudden cardiac death. He was listed for heart transplantation, but was ultimately discharged from the hospital approximately one month after admission given marked clinical improvement. On the day of discharge, his weight had decreased from initial weight of 91 kg to 80 kg, with a recorded total hospital fluid balance of negative 48 liters. At discharge, he was able to ambulate with minimal symptoms and without dyspnea.

Further evaluation for his underlying cardiomyopathy was simultaneously pursued. The clinical history was not suggestive of a viral etiology and viral titers were unrevealing. Testing for metabolic and infectious etiologies was negative. Cardiac magnetic resonance (CMR) imaging demonstrated dilated cardiomyopathy and severe global hypokinesis, without evidence of focal scar or infiltrative process. Further discussion with the patient's family yielded a video taken by the patient's mother, recorded prior to admission. This video was notable for the patient requiring >10 seconds to rise from a seated position, with significant reliance on arm extension to reach an upright position. A thorough neurologic exam was performed, and was significant for 4/5 strength in the knee flexors/extensors, forearm flexors, and wrist flexors/extensors bilaterally.

The patient's age of presentation, severe global hypokinesis on CMR, and motor deficits on exam, all raised the possibility of underlying muscular dystrophy. Electromyography was equivocal for myopathic changes. A biopsy of the vastus lateralis

muscle was significant for moderate-severe myopathic change and extensive single fiber necrosis and fiber size variation. Genetic testing for Duchenne muscular dystrophy and Becker muscular dystrophy was negative. Further molecular testing found the patient to be homozygous for a pathogenic c.826C>A sequence variant in the FKRP gene. He was diagnosed with limb girdle muscular dystrophy type 2I.

The patient remained well in the interim, and at two-year follow-up after the initial hospitalization, he reported minimal symptoms. His LVEF had improved to 30-35%. Cardiopulmonary exercise testing at 2-year follow-up demonstrated a peak oxygen uptake of 10.5 mL/kg and a respiratory exchange ratio of 1.03. He remains very active and currently works as an artist.

Discussion

LGMD encompasses a heterogeneous family of genetic muscle disorders. Patients typically present with proximal greater than distal muscle weakness, though extra-skeletal complications can occasionally be the predominant or presenting symptom. For reasons that remain unclear, patient phenotypes are highly variable with regards to the age of onset, progression of disease, and degree of muscle involvement. While electromyography can reveal myopathic changes in affected muscle groups, the diagnosis of LGMD is generally made after muscle biopsy and molecular gene testing.[1,2] Knowledge of the exact mutations and their locations within particular genes has led to further subdividing within this broad category of muscle dystrophies, beyond simply type 1 (autosomal dominant) and type 2 (autosomal recessive).[2]

The exact frequency of cardiac involvement in LGMD varies with the genetic subtype. To date, the subtype of LGMD most heavily associated with cardiac dysfunction in the literature is LGMD type 2I. Poppe et al. reported cardiac involvement in 21 out of 38 patients (55%) with LGMD type 2I, 8 of whom developed symptomatic heart failure.[3] Similarly, Wahbi et al. observed 23 French patients with LGMD type 2I, 14 (61%) of whom had an abnormal LVEF compared to controls; five of these patients had clinical heart failure.[4] Cardiac dysfunction has also been reported in LGMD types 1A, 1B, 2E, and 2G, and to a significantly lesser extent in types 2A, 2B, and 2D.[1,5-8] Patients with cardiac involvement most commonly exhibit a dilated cardiomyopathy, with or without clinical heart failure.[9-11] Isolated conduction abnormalities have also been reported, particularly atrial fibrillation and non-sustained ventricular tachycardia, which appear to be most prevalent in LGMD type 1B, though case reports of sudden cardiac death in other subtypes exist in the literature.[1,7,11,12]

The degree of cardiac involvement in patients with LGMD generally does not correlate with the degree of skeletal muscle involvement.[4,9,13] Wahbi et al. found no statistical difference in LVEF comparing patients with severe and mild skeletal muscle disease.[4] Similarly, Bourteel et al. observed little correlation between severity of muscular phenotype and severity of cardiac dysfunction in their cohort.[9] Although the small sample sizes in these groups preclude any definite conclusions, these observations and others suggest that severe cardiac involvement can occur in the absence of significant muscle disease. Occasionally, as in the case above and other cases in the literature, the cardiac manifestation is the predominant feature that leads to the diagnosis of an underlying muscular dystrophy.[14,15]

For most patients with LGMD, the extent of cardiac involvement is subclinical at the time of initial presentation and can remain quiescent for years if not decades. Poppe et al. reported 19 patients with LGMD type 2I with definite cardiac involvement on echocardiography, of whom 11 remained asymptomatic during follow-up.[3] In asymptomatic patients, cardiac magnetic resonance (CMR) may uncover subclinical cardiac involvement better than ECG and echocardiography alone, with less operator dependence and better reproducibility between studies.[16,17] CMR abnormalities include left and right ventricular dysfunction and hypokinesis, ventricular enlargement, fatty infiltration/replacement, and late contrast enhancement signifying ventricular fibrosis or scarring.[4,16] Using CMR, Gaul et al. observed cardiac abnormalities in 8 out of 9 patients with LGMD type 2I, compared to 4 out of 9 with echocardiography alone.[16] Similarly, Wahbi et al. observed abnormalities on CMR in 11 out of 13 patients with LGMD type 2I, a higher proportion than the 10-50% that is generally reported as the frequency of cardiac involvement in LGMD.[1,4,18] This suggests that the frequency of cardiac involvement in the various LGMD subtypes may be higher than previously reported, with the greater sensitivity of CMR allowing for enhanced detection of subclinical cardiac dysfunction in otherwise asymptomatic patients.[16]

The detection of cardiac involvement in LGMD patients, even when it is subclinical, can have significant implications. Of 19 patients with LGMD type 2I identified by Poppe et al. as having definite cardiac involvement, 10 patients (52.6%) demonstrated worsening left ventricular function over follow-up of 1-11 years.[3] In the cohort studied by Petri et al., patients with LGMD type 2I experienced a progressive decline in LVEF over a median follow-up of 8.9 years, and LVEF less than 50% was associated with significantly increased mortality.[8] These findings and others highlight the importance of early detection, particularly in high risk LGMD subtypes.[3,8,16] As observed by Poppe et al., implementation of aggressive, guideline-driven heart failure therapy can slow the progression of subclinical cardiac involvement to overt heart failure, though a minority of patients may require cardiac transplantation despite standard medical therapy.[3]

Though no specific guidelines exist at this time, patients with LGMD may benefit from regular cardiac surveillance, particularly those with subtypes more heavily associated with cardiomyopathy. CMR may assist in detection of subclinical cardiac alterations in patients who are otherwise asymptomatic from a cardiopulmonary perspective. More data is needed to better understand the degree of cardiac involvement in the various LGMD subtypes and to guide management decisions.

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