

## A Cardiomyopathy in a Patient With Limb Girdle Muscular Dystrophy Type 2A

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**L**imb girdle muscular dystrophy (LGMD) is a muscular dystrophy with predominantly proximal distribution of weakness that spares the distal, facial, and extraocular muscles early in the course of the disease. Cardiac muscle may be affected, which may manifest as hypertrophic/dilated cardiomyopathy and cardiac dysrhythmias. Significant cardiac involvement has been documented frequently in LGMD2C-F, 2I, and LGMD1B forms of the disease, rarely in the LGMD1C and 2B subtypes, and thus far have not been reported in type 2A. We report a presentation of severe cardiomyopathy in an adult with muscular dystrophy type 2A.

A 23-year-old black man was seen in hospital with complaints of decreased exercise tolerance, dyspnea on exertion, orthopnea, and some presyncopal episodes for several weeks.

The patient's LGMD was diagnosed at the age of 21 years. No family history of similar problems was noted. Physical examination at the time revealed decreased strength in the shoulder girdle area, with inability to raise the arm over the head. Laboratory data at the time showed a creatinine kinase of 4263 U/L and serum troponin of 0.77 ng/mL. ECG revealed sinus rhythm with bifascicular block. The patient's blood was then sent for genetic testing, which demonstrated CAPN3 sequencing alteration (Athena Diagnostics, Inc).

When seen by cardiology, he was noted to be alert and oriented, afebrile, and normotensive. On physical examination he was noted to have jugular venous distension, with cardiac examination significant for a grade III/VI holosystolic murmur at the left lower sternal border, with a displaced point of maximal impulse. ECG revealed normal sinus rhythm, right bundle-branch block, and left anterior fascicular block. Laboratory tests revealed a BNP of 541 pg/mL, with negative cardiac enzymes. His other laboratory tests were found to be within normal limits. An echocardiogram was notable for severely reduced right and left ventricular systolic function, left ventricular ejection fraction of 15%, severe tricuspid regurgitation, and findings suggestive of left ventricular noncompaction (Figure). The patient was treated with ACE inhibitors,  $\beta$  blockers, and diuretics, with no improvement in his cardiac function on subsequent echocardiography. He had few evidence to suggest possible secondary causes of his

cardiomyopathy, including myocarditis and ischemic disease, although he refused more extensive testing.

### Discussion

Significant cardiac involvement has been rarely documented in LGMD1C, 2A, and 2B, whereas it is relatively common in LGMD2C, 2D, 2E, 2F, 2I, and LGMD1B. This may manifest as hypertrophic/dilated cardiomyopathy and cardiac dysrhythmias. LGMD1B patients often exhibit findings of both cardiomyopathy and dysrhythmia.<sup>1</sup>

LGMD2A (calpainopathy) is found as a result of a mutation of chromosome 15 in the CAPN3 gene encoding the proteolytic enzyme calpain-3.<sup>2</sup> Calpain-3 (p94) belongs to the calpain family of soluble intracellular cysteine proteases, the majority of which are activated by a calcium-dependent mechanism. Calpain-3 is not, however, calcium activated, with this expression existing almost solely in muscle, being anchored by titin within the I-band of the sarcomere, at the M line and N2 line.<sup>2</sup> The exact mechanism behind the pathogenesis of LGMD2A is unclear, but it is the most common LGMD of the autosomal recessive variety, comprising  $\approx 30\%$  of cases.

Previous reports have not revealed associated cardiac manifestations in patients with LGMD2A. One postulation to explain this finding is that, despite CAPN3 transcripts being present, there is a lack of calpain 3 expression in adult cardiomyocytes.<sup>3</sup> Our patient clearly exhibits CAPN3 sequencing alteration on genetic testing and is now diagnosed with new ventricular dysfunction of no other clear pathogenesis, at the age of 23 years. He was also noted to have findings suggestive of left ventricular noncompaction that has also been linked to genetic mutations responsible for various neuromuscular disorders, including the LMNA gene giving rise to limb girdle muscular dystrophy.<sup>4</sup> It is unclear whether the manifestation of cardiomyopathy in our patient demonstrates new possible mechanisms in the pathogenesis of LGMD2A or a variant of a previously described pathway. The association of cardiomyopathy in our patient with LGMD2A is, however, an important one, which has not been demonstrated in previous studies. Further investigation may indicate a larger prevalence of cardiomyopathy in this population.

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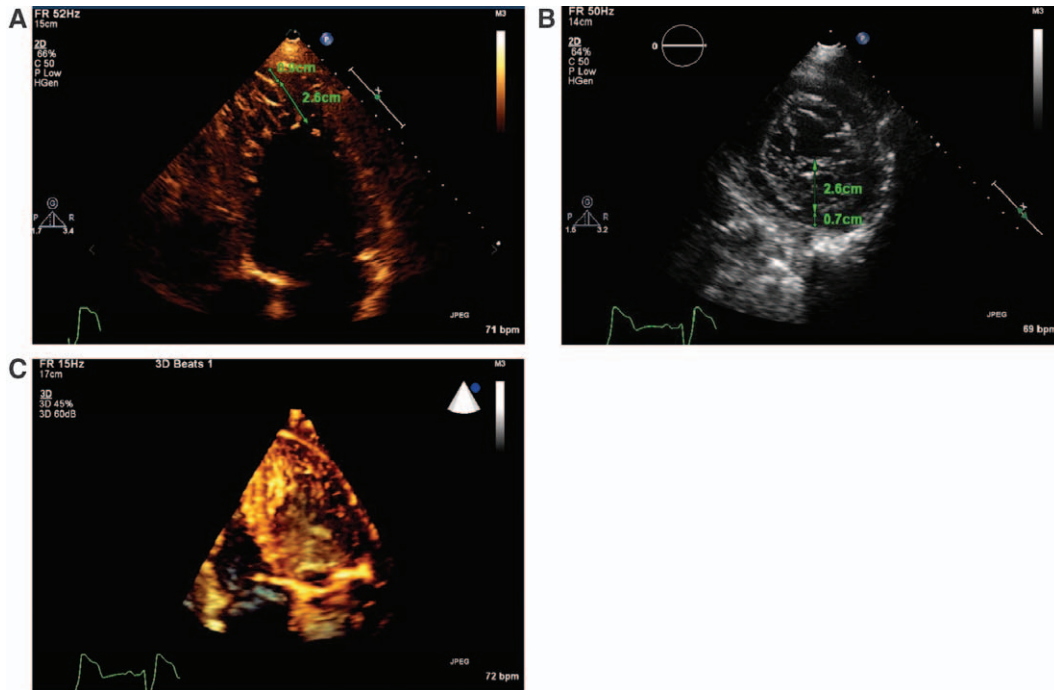
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**Figure. A–C,** Echo showing patient's left ventricular noncompaction (see **green arrows** for comparison with left ventricular wall thickness). **A,** Apical 4-chamber view in systole. **B,** Parasternal short axis view in systole. **C,** Three-dimensional apical 4-chamber view.

## Disclosures

None.

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**KEY WORDS:** cardiomyopathy ■ genetics