Case Report

Cardiac Disease in Limb-girdle Muscular Dystrophy Type 2

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ABSTRACT

Limb-girdle muscular dystrophy is a rare inheritable muscle disease, and cardiovascular involvement is of prognostic significance. Only a few cases have been reported in our population. We, therefore, present the case of a 20-year-old student who was referred to the cardiac clinic on account of cardiomegaly on routine chest X-ray. He had dyspnoea on exertion, and occasional palpitations. There was a history of difficulty with standing from a sitting position, climbing stairs and raising his upper limbs above his head. His younger sister also has difficulties performing these tasks but has no cardiac symptoms. On examination, there was bilateral proximal muscle weakness with severe atrophy and an abnormal gait. There was sinus bradycardia on electrocardiography. Echocardiography revealed dilated cardiac chambers with ventricular dysfunction.

Key words: Cardiac, disease, dystrophy, muscular

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INTRODUCTION

Limb-girdle muscular dystrophies (LGMDs) are a genetically and clinically heterogeneous group of muscle diseases which predominantly affects the proximal muscles (pelvic and shoulder girdle musculature).[1] They are rare neuromuscular diseases with an estimated prevalence of 1 in 23,000–1 in 150,000.[2,3]

Other forms of muscular dystrophies include the more common Duchene and Becker's muscular dystrophy (dystrophinopathies), Emery–Dreifuss muscular dystrophy, myotonic dystrophy, congenital muscular dystrophy and facioscapulohumeral muscular dystrophy.

LGMD are caused by mutations in genes that encode for various muscle membrane proteins such as dystrophin-associated glycoprotein, sarcomeric and nuclear membrane proteins some of which are expressed in both skeletal and heart muscle.

The skeletal muscles are primarily affected, but the myocardium as well as the specialized conducting myocardial fibres may be involved in the dystrophic process in the form of cardiomyopathy and conduction defect, respectively. The frequency and severity of cardiac involvement vary with different types of muscular dystrophies. Cardiac involvement is not necessarily related to the degree of skeletal myopathy and may even be the presenting or pre-dominant symptom.[4]

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Cardiovascular disease in LGMD is of prognostic significance as patients usually succumb to fatal arrhythmias (sudden death) or progressive heart failure. Besides the case reported in facioscapulohumeral muscular dystrophy by Anisiuba *et al*.,[5] there are only a few reports of cardiac diseases in muscular dystrophy in our population. We, therefore, present a case of cardiac disease in LGMD in a family where 2 siblings have the disease, but only one has cardiac features.

CASE REPORT

Mr. E M, a 20-year-old undergraduate student was referred to the cardiac clinic on account of cardiomegaly on chest X-ray, which was performed for medical clearance on admission into tertiary institution. He had a 1 year history of easy fatigue, dyspnoea and palpitations on exertion. Episodes of palpitations were not associated with chest pain, dizziness or syncope. There was no history of orthopnoea, paroxysmal nocturnal dyspnoea, cough or leg swelling. He had never been diagnosed of any form of cardiac disease. There is no known family history of cardiac disease or premature death.

He also complained of difficulty with standing from a sitting or squatting position, climbing stairs and raising his upper

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limbs above his head. These symptoms have progressed to affect his gait, now walks with an abnormal gait (waddlimg) associated with lower back pain. His immediate younger sister has similarly complaints of proximal muscle weakness and an abnormal gait but no cardiac symptoms. Both parents and the other four siblings are not affected. There is no known history of parental consanguinity or similar complaints in the extended family members. Infancy and childhood were unremarkable and developmental milestones were not delayed. His academic performance has been satisfactory.

There is no history of recurrent fever, muscle pain or skin rash. There are no recurrent falls, dysphasia, respiratory or speech difficulty, and he has never had a seizure or stroke. He is not a diabetic or thyroid disease patient, and he does not take alcohol or steroids.

Examination revealed a young man with a small frame. His height was 1.65 m and he weighed 50 kg (body mass index of 18.27 kg/m^2). Neurologic examination revealed bilateral, symmetrical wasting of the pectoral and pelvic muscles with associated reduced muscle power in the proximal limb girdle group [Figure 1]. The tendon reflexes were normal. Sensory and cerebella examination were also normal; he, however, had a waddling gait. Younger sister had similar but more severe muscle weakness. Both parents and the other siblings also had a neurologic examination, but there were no abnormal findings.

The pulse rate was 58 beats per minute, of normal volume and regular. The blood pressure was 110/70 mmHg. The apex beat was displaced to the 5th left intercostal space lateral to the mid clavicular line. Only the first and second heart sounds were present. The lung fields were clear and the liver was not palpable.

A chest X-ray confirmed cardiomegaly [Figure 2] and electrocardiography (ECG) revealed sinus bradycardia with prominent R waves in right precordial leads (V1–V2) [Figure 3]. There was left ventricular hypertrophy by Sokolow-Lyon voltage criteria (SV1 + RV5).

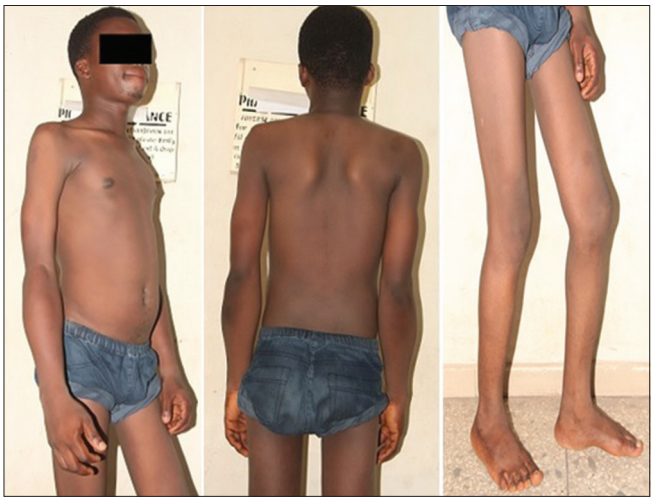

Figure 1: (a) Atrophy of pectoral and arm muscles. (b) Winging of both scapulae. (c) Atrophy of thigh muscles

Abnormal findings on echocardiography include an enlarged right ventricle and atrium. The major and minor dimensions of the right ventricle were 6.16 and 4.35 cm, respectively. The right ventricular systolic function was impaired. Tricuspid annular plane systolic excursion (TAPSE) was 1.39 cm [Figure 4].

Left ventricular dimensions were as follows:

- Interventricular septal thickness in diastole - 0.93 cm
- Left ventricular internal diameter in diastole - 4.61 cm
- Left ventricular posterior wall in diastole - 0.83 cm
- Interventricular septal thickness in systole - 1.01 cm
- Left ventricular internal diameter in systole - 2.94 cm
- Left ventricular posterior wall in systole - 1.27 cm.

Ejection fraction = 62%. This good systolic function most probably represents an increased stroke volume needed to compensate for the bradycardia to maintain cardiac output. The mitral valves were competent. The right ventricular systolic function was impaired. There was Grade 3 diastolic dysfunction (E/A ratio = 2.81) [Figure 5].

Histology of muscle biopsy revealed the variation of fibre sizes with atrophy. There were also amorphous necrotic muscle fibres with areas of regeneration (dystrophic changes). The level of creatine kinase was markedly elevated 411 IU/L (reference range of 10–80 IU/L).

A diagnosis of LGMD2-I with cardiomyopathy was made based on the distribution of muscles weakness, family history and mode of inheritance (autosomal recessive). The genetic Subtype I was predicted by the automated LGMD diagnostic assistant (http://www.jain-foundation.org/lgmd-subtyping-diagnosis-tool). This is a diagnostic tool designed to help physicians predict the most likely type of LGMD a patient may have based on the clinical presentation and laboratory findings. This tool was applied because genetic studies are not available in our setting.

He is currently on anti-platelets and loop diuretics. He has been informed about the need for a pacemaker when he becomes symptomatic of the bradycardia. He is to have 6 monthly

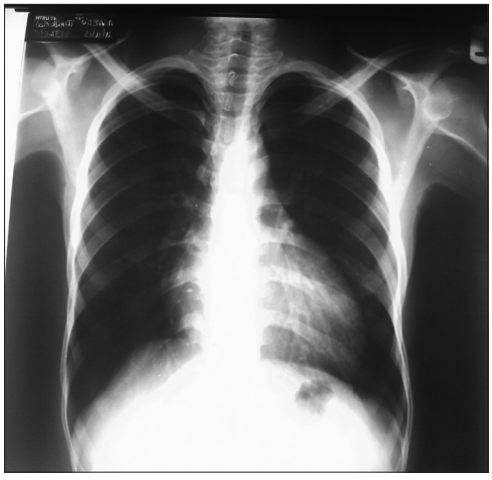

Figure 2: Chest radiograph (posteroanterior view): Showing cardiomegaly

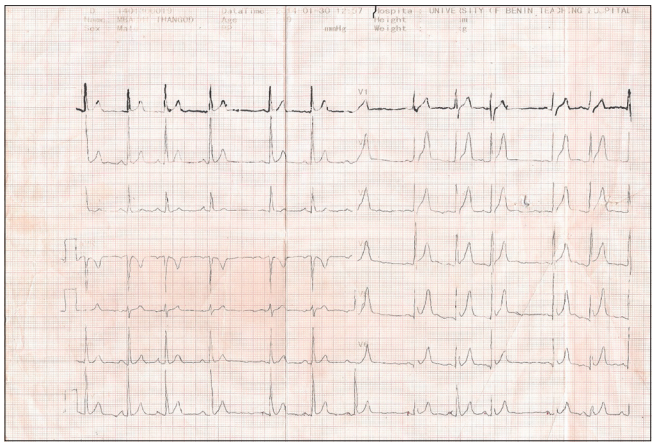

Figure 3: Electrocardiogram showing sinus bradycardia, and prominent R-waves in leads V1–V2

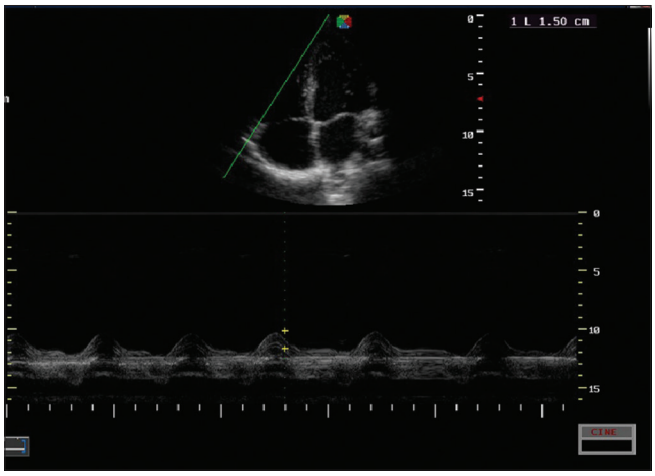

Figure 4: Reduced tricuspid annular plane systolic excursion

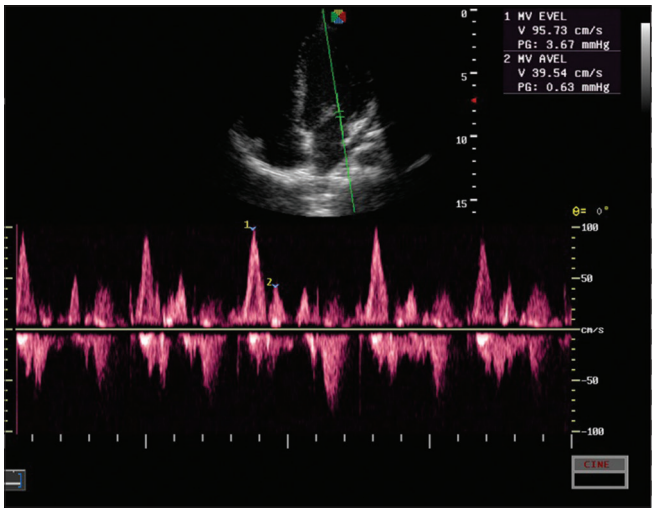

Figure 5: Transmitral flow Doppler: Left ventricular diastolic dysfunction

cardiac monitoring with ECG and echocardiography. The patient and his family members have been informed about the nature, inheritance and implications of the disease (genetic counselling).

DISCUSSION

LGMD is inherited either as an autosomal dominant disease (LGMD1) or autosomal recessive (LGMD2). The more common LGMD2 generally has an earlier age of onset, worse symptoms and more rapid progression compared to LGMD1. There are different genetic subtypes of LGMD2 (2A – 2M) based on the deficient muscle protein.

Clinical presentation is highly variable as different muscle proteins are affected. Distinct mutations may result in a clinically indistinguishable phenotype whereas strikingly different phenotypes may be due to identical gene mutations. Patients generally present with slowly progressive weakness and wasting restricted to the proximal muscles.

The occurrence of the cardiac disease varies with the genotype. LGMD 2C–2F (sarcoglycanopathies) and LGMD2I have been associated with cardiac disease. There is, however, no clear evidence of cardiac involvement in LGMD2A and LGMD2B.[6] Limb-girdle type 2G, 2H, 2J, 2K 2L and 2M have only been recently described and have thus far not been associated with cardiac abnormalities.[6]

LGMD2I is caused by mutations in the gene[7] which encodes an enzyme glycosyltransferase, required for glycosylation of the transmembrane protein a-dystroglycan in muscle cells.

Sveen *et al*.[8] reported cardiac involvement in 29% of LGMD2I patients. Left ventricular wall motion abnormalities and dilated cardiomyopathy started as early as the teen years. A substantial proportion of patients developed symptomatic cardiac failure over time, starting at a mean age of 38 years (range 18–58).[9] Cardiac disease did not correlate with age, muscle strength or the level of dystrophic changes on muscle biopsy. Other cardiac abnormalities reported in LGMD2I include ECG changes such as dysmorphic notched P-waves, Q-waves in lateral leads and complete or incomplete right or left bundle branch block. Dilated cardiomyopathy was associated with a considerable risk of cardiac death at an age range of 16–67 years.[9] This index case also presented with features of dilated cardiomyopathy. There was, however, no bundle branch block on ECG.

In a study of 23 patients with LGMD2I by Wahbi *et al*.,[10] echocardiography revealed impaired left ventricular contractility in 14% of the patients. Functional and morphological ventricular abnormalities, including ventricular wall fibrosis and fatty replacement, were found in 57% of the patients on cardiac magnetic resonance imaging.

Cardiac disease has also been reported in LGMD2C-F. In a study of 97 patients with LGMD in The Netherlands, van der Kooi *et al*.[11] reported clinically relevant cardiac abnormalities in 10% of cases. The abnormalities were dilated cardiomyopathy and atrioventricular conduction defects.

Politano *et al*.[12] also reported arrhythmogenic cardiomyopathy in 6.3% and initial signs of dilated cardiomyopathy in 18.7% in a study of twenty patients with sarcoglycanopathies in Italy. Six (35.3%) of the patients had ECG signs of pulmonary

hypertension, ventricular ectopic beats and sustained paroxysmal sinus tachycardia. Others include inverted T-waves; tall R-waves in leads V1-V2 which this patient had and deep Q-waves in V4–V6.

The absence of cardiac disease in the younger sister who even had more disabling muscle weakness is in support of the earlier observation that the development of cardiac features bears no relationship with the severity or degree of skeletal myopathy.

LGMD is a progressive and disabling muscle disease as most patients loose mobility and become dependent on wheelchair within 20–30 years of symptom onset. The presence of cardiovascular disease portends a worse outcome compared to those without cardiac involvement. All cases of muscular dystrophy should, therefore, be screened for cardiovascular disease since the typical signs and symptoms of cardiac dysfunction may not be present, due to the patient's muscular impairment and limited mobility. Prompt institution of the appropriate intervention helps avert complications such as sudden cardiac death.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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