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CASE REPORT

A Patient of Limb-girdle Muscular Dystrophy Type 1B Presenting with Heart Failure and Cardiac Conduction Defects: A Case Report

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Abstract

Background: Limb-girdle muscular dystrophy type 1B (LGMD1B) are characterised by cardiac dysrhythmias, late-onset cardiomyopathy, slowly progressive skeletal myopathy and contractures of the neck, elbows and ankles. The causative mutation is in lamin A/C gene (autosomal dominant LGMD1B).

Objective: To assess the clinical outcome of a patient of limb-girdle muscular dystrophy type 1B with heart failure and cardiac conduction defects.

The case: We report a case of 47-yr-old male with proximal muscle weakness who presented with repeated exertional dyspnea and repeated presyncope. ECG revealed junctional bradycardia. Echocardiography revealed global wall motion abnormality with EF 48%. EMG showed myopathic pattern. Next genome sequencing showed that the patient has a missense mutation in exon 4 region of LMNA gene (c.G662A/p.Arg221His). Cardiac involvement is very common in this disease which includes AV block, bradycardia, atrial tachycardia, atrial fibrillation and ventricular dysrhythmia causing sudden death. Our patient presented with symptomatic junctional bradycardia which necessitates implantation of permanent pacemaker.

Conclusion: Cardiologists should be aware of these unusual genetic diseases with conduction defects, especially in young adults.

Keywords: Muscular dystrophies; Cardiomyopathies; Lamins; Heart conduction system

Introduction

Limb-girdle muscular dystrophy LGMDs are a heterogeneous group of genetically determined by progressive disorders of skeletal muscle with a primary or predominant involvement of the pelvic and shoulder girdle musculature. Because of their heterogeneity and the lack of diagnostic speciûcity, there are few reports on the prevalence of LGMD. Estimates for prevalence of all forms of LGMD range from one in 14,500 to one in 123,000. [1] Limb-girdle muscular dystrophy type 1B is characterised by progressive limb-girdle weakness (affecting the pelvic before shoulder girdle), mild joint contractures, atrioventricular cardiac conduction disturbances, and cardiomyopathy. The disease is due to mutations in the LMNA gene, encoding lamins A/C.[2] Respiratory muscle involvement is frequently observed in patients with limb girdle muscle dystrophy, mild dyspnoea on exertion, chronic cough, and recurrent respiratory tract infections having been reported.[3,4] The long-term outlook for people affected by limb-girdle muscular dystrophy type 1B depends on the signs and symptoms present in each person. In general, LGMD1B is a slowly progressive disease, meaning the muscle weakness can continue to worsen eventually. If the cardiac abnormality associated with the disease are not properly evaluated, monitored and treated, people with LGMD1B are at risk to have sudden cardiac death.[5] Some people with LGMD1B have successfully been treated with cardiac transplantation .[6]

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The Case:

On 19 September 2019, a 47-year-old male hailed from Barishal, presented with dizziness for two episodes lasting for about 5 minutes which were

preceded by palpitation and associated with lightheadedness. Dizziness were self-limiting and not associated with change in posture or fall, chest pain, slurring of speech or weakness of any part of the body. There was no headache, tinnitus, history of fall, nausea, vomiting or diplopia. He gave a history of NYHA II dyspnoea for two months prior to this presentation. Dyspnoea was not associated with wheeze or any seasonal variation. There was no history of orthopnea or paroxysmal nocturnal dyspnoea. He was suffering from weakness and wasting of proximal muscles of both upper and lower limbs from 8 years of age; which was insidious in onset and slowly progressive. He had difficulty in climbing stairs, running, getting up from sitting and squatting position, heavy weight lifting and raising arms above the head. However, there was no history of distal muscle weakness, twitching of the muscles or pain in the limbs. There was also no dysarthria, dysphonia, diplopia or sensory symptoms and no bladder- bowel disturbances. He had no history of addictions or drug intake. He is the fourth child born of non-consanguineous marriage. Birth history and developmental milestones were normal. Family history revealed that his two younger brothers died from cardiac problem at 41 years and 45 years of age respectively; both suffered from similar weakness in limbs since their 10-12 years of age.

General physical examination of our patient was normal. Neurological examination showed normal higher psychic functions, intact cranial nerves with normal fundus. He had wasting of both shoulders, and thighs (figure 1), and hypotonic all four limbs. Power

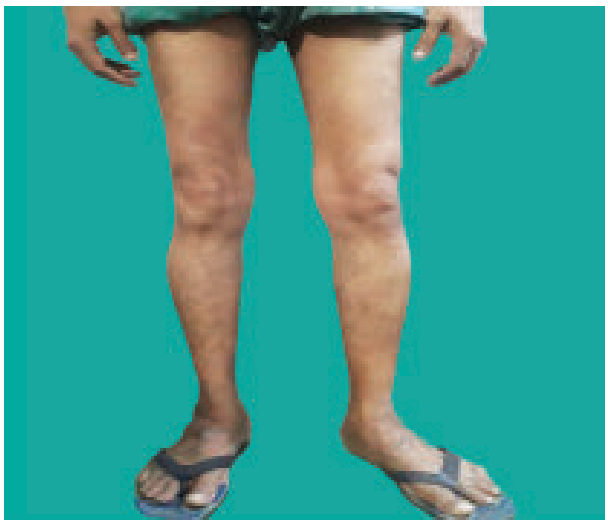

Figure-1: Wasting of both lower limbs muscle

was 3/5 at both shoulders, 4/5 at both elbows, 5/5 at both wrists, 3/5 at both hip joints, 3/5 at both knees, 5/5 at both ankles. Winging of the scapula was present (figure 2). Deep tendon reflexes and superficial reflexes were normally present with bilateral flexor plantar

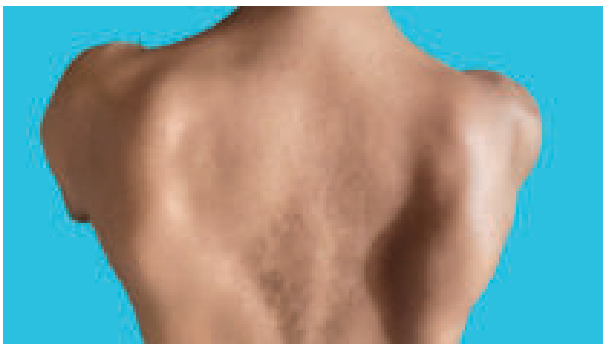

Figure 2: Winging of the scapula

response. Sensory system was normal. He had waddling gait. There were no cerebellar signs and skull and spine was normal. Cardiovascular examination showed pulse 44 bpm, regular, large volume and normal character with no radio-radial or radio-femoral delay, BP-110/60 mmHg in both arm with no postural drop, JVP examination showed large a wave simulating cannon wave. Apex beat was located in 6th ICS 10 cm away from midline and diffuse in nature, 1st heart sound was soft and a 3rd heart sound was audible, there was a soft systolic murmur in apical area. Respiratory, abdominal and ophthalmological examination were unremarkable.

Investigations showed normal haemogram (Hb% -12.9 g/dl, TC of WBC- 7520 /cmm, DC of WBC:N/L/M/E-60/35/2.8/1.1,Platelet:291000/cmm, ESR:22 mm in 1st hour),liver function(SGPT-22 U/L,ALP-74 U/L),renal function (serum creatinine 0.81 mg/dl) and serum electrolytes(Na-138 mmol/l,K-4.8 mmol/l,Cl-100 mmol/l), thyroid function test (FT4-1.23 ng/dl,S.TSH:0.969 mIU/L),serum cortisol(238 nmol/L) and serum LDH (165 U/L). Creatinine phosphokinase was 70 IU/l. (Reference: 55-170 U/L). Urine routine examination was normal. Chest X-ray, and USG of abdomen were normal. Electrocardiography showed Junctional Bradycardia (HR 44bpm) with complete right bundle branch block (RBBB) with right axis deviation (RAD) due to left posterior hemiblock (LPHB) (figure-3). Echocardiographic findings showed dilated cardiomyopathy. The ejection fraction of the left ventricle was 48% and end diastolic and end systolic diameter of the left ventricle was 58 mm (figure 4) and

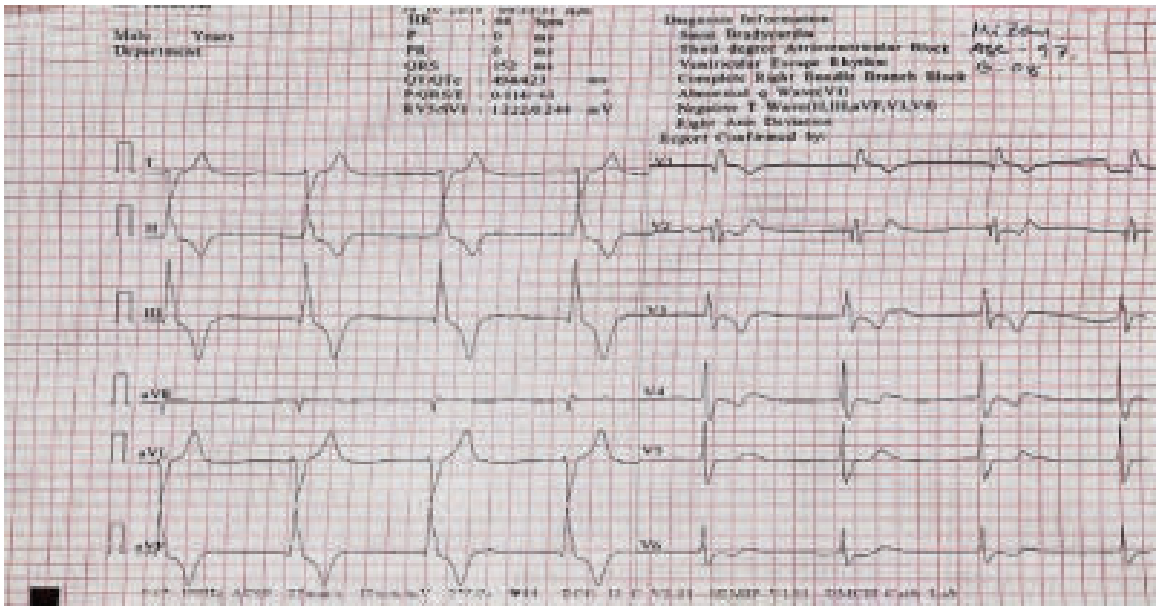

Figure 3: *ECG showed junctional bradycardia (HR-44bpm) with complete RBBB with RAD due to LPHB*

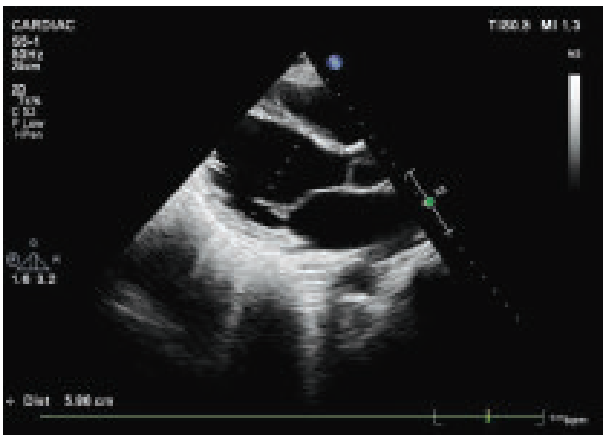

Figure 4: Echocardiography revealed dilated left ventricle

39 mm respectively. Nerve conduction study was normal. EMG performed in right upper and lower limb showed myopathic pattern. Muscle biopsy from right quadriceps muscle revealed increased fatty tissue with relatively reduced number of muscles fibres. Genetic studies and DNA analysis showed that the patient has a missense mutation in exon 4 region of LMNA gene (c.G662A/p.Arg221His).

We admitted our patient in coronary care unit of Dhaka Medical College Hospital on 23 October 2019, and stayed till 10 November 2019. Heart failure symptoms was controlled with diuretics and angiotensin-converting-enzyme inhibitor. After initial stabilization dual chamber permanent pacemaker (PPM) was implanted. Appropriate physical therapy was given to the affected skeletal muscle including occupational therapy. He was followed up six months later and was absolutely free of any previous symptoms. Left ventricular function and dilatation was improved as assessed by echocardiography. Now he is doing well with his daily activities.

Discussion

Limb-girdle muscular dystrophy type 1B (LGMD1B) is a variety of limb-girdle muscular dystrophy. These diseases affect the voluntary muscles, which are responsible for movement on purpose, such as the legs, arms, toes, fingers and facial muscles. Specifically, LGMD1B causes muscle weakness significantly in the lower limbs. The muscle weakness typically affects the muscles closest to the center of the body (proximal muscles) such as the thighs and shoulders including girdle muscles. The disease is progressive, leading to a loss of muscle strength and bulk over a number of years. Limb-girdle muscular dystrophy type 1B is caused by mutations to the LMNA gene. The disease is inherited in an autosomal dominant manner. Our patient had 2 brothers who died previously from similar illness. A diagnosis of LGMD1B is suspected in people who have signs and symptoms consistent with the disease, and the diagnosis can be confirmed with laboratory tests including genetic analysis. The symptoms of

LGMD1B can begin at any time between childhood and adulthood. About half of all affected individuals show signs of the disease in childhood. Other symptoms of the disease may include difficulty straightening the elbows (elbow contracture) and heart problems including arrhythmia or cardiomyopathy . The signs and symptoms of people with LGMD1B can vary, even among members of the same family.[5]

The syndrome of LGMD represents more than one disorder. Both males and females are affected with onset ranging from late in the ûrst decade to the fourth decade. Respiratory insufûciency from weakness of the diaphragm and cardiomyopathy may occur. A systemic classification is based on autosomal dominant (LGMD 1) and autosomal recessive (LGMD 2) inheritance. Presently there are seven autosomal dominant and 10 autosomal recessive disorders LMNA, also known as Lamin A/C is a protein that is encoded by the LMNA gene in human being.[7-9] Next generation sequencing revealed an additional, heterozygous mutation, affecting exon 4 of the LMNA gene (c.G662A/p.Arg221His) of our patient. Mutations of LMNA are associated with at least 8 different phenotypes, including Emery-Dreifuss muscular dystrophy, limb girdle muscular dystrophy 1B, dilated cardiomyopathy, familial partial lipodystrophy, Charcot- Marie-Tooth neuropathy type 2B1, mandibuloacral dysplasia, and Hutchinson Gilford as well as atypical Werner progeria syndromes.[1011] Although genotype-phenotype correlation has been attempted there is a striking intra-familial and inter-familial phenotypic heterogeneity, which may be partly ascribable to the variable genetic backgrounds.[12-13] EDMD is phenotypically more similar to LGMD 1B and is characterized by a triad of early contractures (Achilles tendon, elbows, and posterior cervical muscles), Progressive atrophy of humeroperoneal distribution and cardiac conduction defects.[14] Charcot-Marie-Tooth disease type 2B1 is an axonal disorder of the peripheral nervous system, characterized by progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms with normal or slightly reduced nerve conduction velocities, and progressive distal muscle weakness and atrophy. Unfortunately, there is no cure for limb-girdle muscular dystrophy type

1B (LGMD1B). Treatment options include weight control to avoid obesity, physical therapy and stretching exercises to prevent contractures of the elbows, use of mechanical aids such as canes, walkers, and wheelchairs and monitoring for evidence of heart rhythm problems. In some cases, a permanent pacemaker may be necessary to treat heart problems associated with LGMD1B.[5] We have treated our patient with implantation of a dual chamber permanent pacemaker for symptomatic junctional bradycardia along with physiotherapy for muscular involvement.

Conclusion

Our case describes autosomal dominant LGMD IB with positive family history, normal creatinine phosphokinase and diagnostic EMG, muscle biopsy and next genome sequencing. Onset, progression and distribution of the muscular and cardiac involvement vary considerably among individuals and genetic subtypes. Suspicion for LMNA mediated cardiomyopathy should arise in patients with extracardiac manifestations of laminopathies and genetic analysis eventually confirms the underlying diagnosis

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