

Case Report

Limb Girdle Muscular Dystrophy with Cardiac Conduction Block

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Abstract

Introduction: Limb-girdle muscular dystrophy refers to disorders that cause wasting and weakness of the muscles around the shoulders and hips with autosomal pattern of inheritance. Most common features are muscle weakness and atrophy, myoglobinuria, myotonia, elevated serum kinase, and cardiomyopathy in about 20% cases.

Case Report: We report a sporadic case in an 18 year old male patient, who presented with complaints of difficulty in walking on toes, squatting, climbing stairs and breathlessness on exertion since 6 months. Examination revealed weakness of shoulder girdle and hip muscles bilaterally with achilles tendon contractures. Investigations revealed creatine kinase of 1870IU/L, normal blood counts, ESR and CRP. Thyroid profile was normal. MRI spine was normal. Nerve conduction study was normal. Electromyography showed short duration, low-amplitude motor unit potentials, increased proportion of polyphasic potentials, and early recruitment with a full interference pattern. ECG showed incomplete left bundle branch block. Echocardiography showed generalized hypokinesia with ejection fraction of 40%. Quadriceps muscle biopsy confirmed muscular dystrophy.

Conclusion: Cardiac conduction abnormalities are rarely reported in cases of limb girdle muscular dystrophy. Automated LGMD Diagnostic Assistant (ALDA) suggests patient has medium probability and concordance of LGMD subtypes LGMD2G (36.90) and LGMD2I (23.92). Genetic study confirmed LGMD2G.

Keywords: Distal muscular atrophy; proximal muscle weakness; Contracture; Incomplete Left Bundle Branch conduction block

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Introduction

Limb-girdle muscular dystrophy (LGMD) was first proposed as disorder in 1954 by Walton and Natrass [1]. Overall frequency of all LGMD syndromes is estimated to be 5-70 per 1 million population in several countries [2]. LGMD is reported in all countries affecting both males and females equally [3]. LGMD commonly leads to wheelchair dependence within 20-30years of symptom onset with high inter-patient variability [4]. Age of onset is usually between 10 and 30years. There are more than 20 different subtypes of LGMD as of 2012[5].

Limb-girdle muscular dystrophy (LGMD) protein defects manifest in several pathways that involve in the muscle biologic function and can be divided based on cellular localization into groups. These include proteins associated with the sarcolemma, contractile apparatus and enzymes involved in muscle function. Precise mechanism causing dystrophic phenotype was not clearly established in all cases. LGMD2B is relatively common and accounts for 3-19% of all LGMDs. LGMD2I is common in Northern Europe (Denmark and parts of England), but globally frequency of occurrence outside these areas account for 3-8% of all LGMDs.

The sarcoglycanopathies as a group (LGMD2C-LGMD2F) account for 3-18% of LGMDs, with a high percentage of severe cases. LGMD2C occurs more common in Tunisia; LGMD2D in Europe, USA, and Brazil; and LGMD2E and LGMD2F in Brazil. Overall, LGMD2D (α -sarcoglycanopathy) is twice as common as LGMD2C (γ -sarcoglycanopathy) and LGMD2E (β -sarcoglycanopathy), and LGMD2F (δ -sarcoglycanopathy) is the rarest.

LGMD2B constitutes more common cause of autosomal recessive LGMD, accounting for about 20% of cases in the Brazilian population. In Some people (eg, Cajun, Arcadian groups), it accounts for about 40% of cases. Several phenotypes include Miyoshi myopathy, anterior tibial myopathy, LGMD, and an axial myopathy. A study from France showed 25% with Miyoshi myopathy, 25% with LGMD, and 35% with a combination [6].

Autosomal recessive limb girdle muscle dystrophy is caused by following mutations where the number in bracket represents gene or locus MIM (Mendelian inheritance in man) number. LGMD2B (253601) is caused by mutation in the dysferlin gene (DYSF; 603009) on 2p13; LGMD2C (253700) caused by mutation in the gamma-sarcoglycan gene (SGCG; 608896) on 13q12; LGMD2D (608099) caused by mutation in the alpha-sarcoglycan gene (SGCA; 600119) on 17q12; LGMD2E (604286) caused by mutation in the beta-sarcoglycan gene (SGCB; 600900) on 4q12; LGDM2F (601287) caused by mutation in the delta-sarcoglycan gene (SGCD; 601411) on 5q33; LGMD2G (601954) caused by mutation in the TCAP gene (604488) on 17q12; LGMD2H (254110) caused by mutation in the TRIM32 gene (602290) on 9q31; LGMD2I (607155) caused by mutation in the FKRP gene (606596) on 19q13; LGMD2J (608807) caused by mutation in the titin gene (TTN; 188840) on 2q24; LGMD2K (609308), caused by mutation in the POMT1 gene (607423) on 9q34; LGMD2L (611307), caused by mutation in the ANO5 gene (608662) on 11p14; LGMD2M (611588), caused by mutation in the FKTN gene (607440) on 9q31; LGMD2N (613158), caused by mutation in the POMT2 gene (607439) on 14q24; LGMD2O (613157),

caused by mutation in the POMGNT1 gene (606822) on 1p34; LGMD2Q (613723), caused by mutation in the PLEC1 gene (601282) on 8q24; LGMD2R (615325), caused by mutation in the DES gene (125660) on 2q35-q36; and LGM2S (615356), caused by mutation in the TRAPPC11 gene on 4q35.

Case Report

We present a case report of an 18-year-old male who presented with proximal weakness in both upper limbs and lower limbs since 6 months, which was insidious in onset and gradually progressive. Patient complained of difficulty in walking on toes, climbing stairs, getting up from squatting position, running, and raising arms above the head. There was thinning of shoulders, arms and thighs. History of breathlessness on exertion since 6 months after walking more than 400 meters or climbing 3 floors of stairs is present.

No history suggestive of distal muscle weakness, twitching of the muscles or pain in the limbs. No history suggestive of cranial nerve involvement or sensory symptoms. No history of bladder and bowel disturbances. No history of drug intake. Not a smoker or alcoholic or any other addictions. He is the first child born out of non-consanguineous marriage during a normal delivery in a hospital. Infancy period was uneventful. Psychomotor development was normal.

Family history revealed no similar complaints. General physical examination was normal except with single breath count of 34. Higher mental functions were normal. No Cranial nerve abnormalities observed. Speech was normal. Atrophy of bilateral shoulders with wasting of Deltoids (Figures 1 and 2), atrophy of pelvic girdle muscles (Figure 3) was present. No pseudo hypertrophy was noted in calf muscles (Figure 3). Hypotonia was present in all four limbs. Power 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, 3/5 at both ankles.



Figure 1 Atrophy of shoulder muscles



Figure 2 Shoulder muscles atrophy



Figure 3 Atrophy of Pelvic girdle muscles without Calf hypertrophy and Achilles tendon contractures

All deep tendon reflexes were absent bilaterally except for ankle jerk which was present. Superficial reflexes were present with plantar reflexes showing bilateral flexor response. Sensory system was normal. Waddling gait was present. There were no cerebellar signs, skull and spine was normal. Respiratory, cardiovascular and abdominal examination was normal.

Electrocardiogram showed incomplete left bundle branch conduction block (Figure 4). Laboratory findings were as follows: CK: 1870 U/L, CK-MB: 32 U/L, Troponin: negative and echocardiography showed generalized hypokinesia with an ejection fraction of 40%. Investigations revealed total white blood cell count of $5000/\text{mm}^3$, Hemoglobin of 12.3mg/dl and platelet count was $200000/\text{mm}^3$. The arterial blood gases had pH of 7.37, a PO₂ of 85 mmHg, PCO₂ of 30mmHg and 17 mmol/l of bicarbonate. Urine routine and urine for myoglobin was negative. Renal function test was normal with creatinine of 0.6mg/dl and blood urea of 31mg/dl. Liver function test was normal.

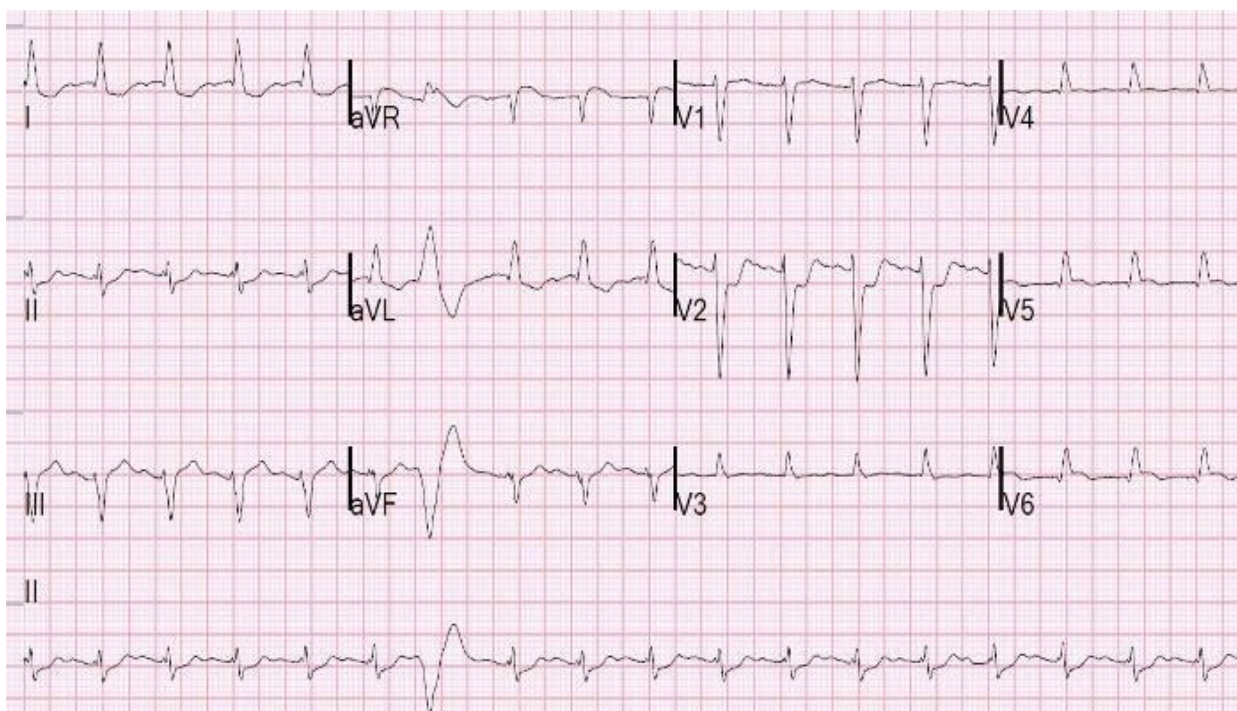


Figure 4 ECG showing incomplete Left Bundle branch block

Thyroid profile was normal. MRI spine was normal. Nerve conduction study was normal. Electromyography showed short duration, low-amplitude motor unit potentials, increased proportion of polyphasic potentials, and early recruitment with a full interference pattern. Muscle biopsy from left quadriceps muscle showed preserved fascicular architecture with marked variation in fibre size. There is evidence of hypertrophy, rounding, internal nuclei, myophagocytosis and occasional necrotic fibres. MAT- highlights the endomyseal fibrosis. MGT- No ragged red fibres or rimmed vacuoles. SDH, NADH- No moth eaten or lobulated fibres. ATPase 4.6 and 9.4- Type 1 fibre pseudo grouping noted. Biopsy confirmed the diagnosis of Muscular Dystrophy (Figure 5 and 6).

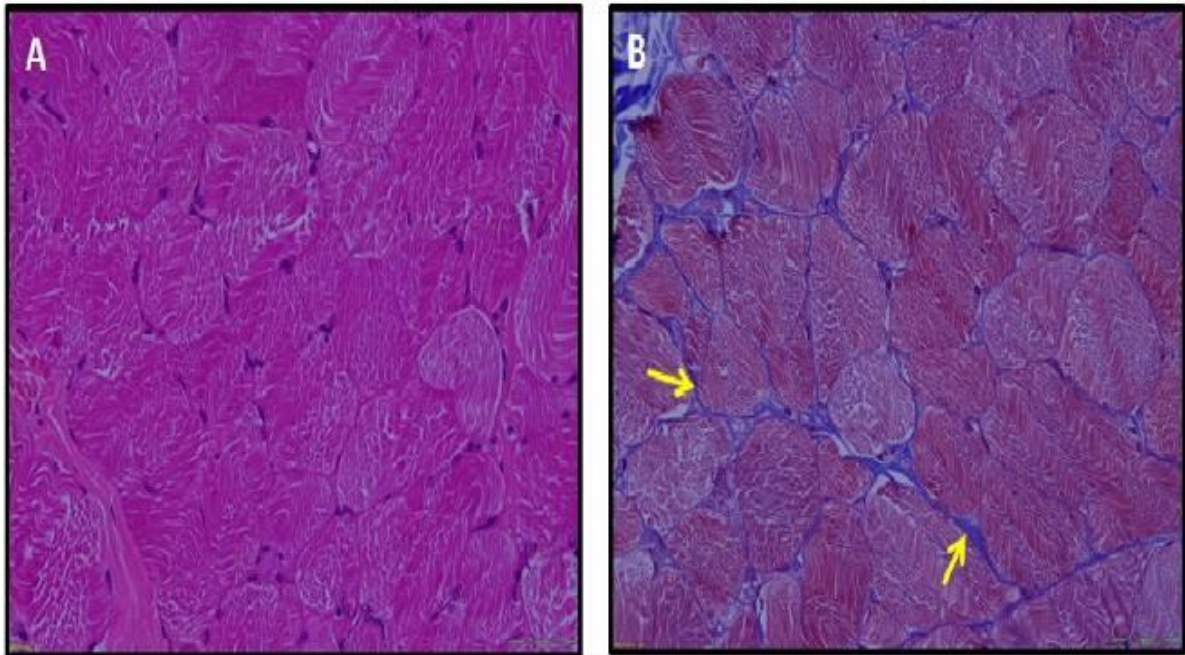


Figure 5 Left Quadriceps Muscle Biopsy showing muscular dystrophy. Transversely cut skeletal muscle tissue showing: A. variation in diameter and rounding of fiber (HE); B. variation in diameter, rounding of fiber and mild endomyseal fibrosis \uparrow (MAT)

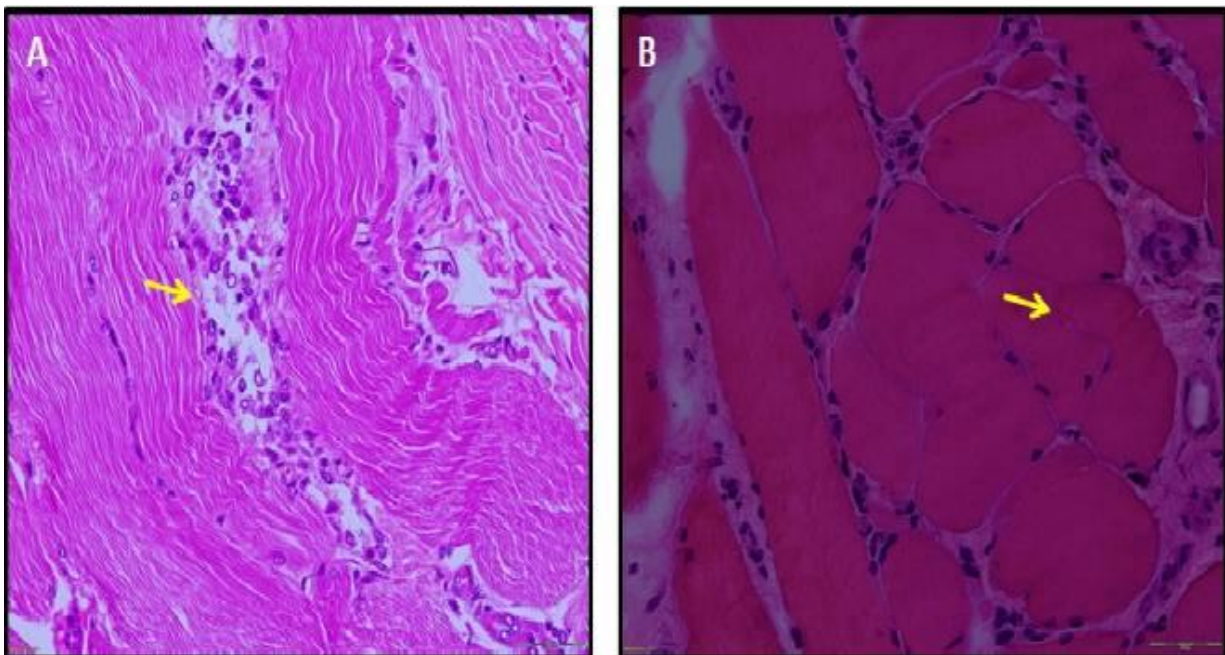


Figure 6 Muscle Biopsy from left quadriceps muscle; Transversely cut skeletal muscle tissue showing: A. Myophagocytosis \uparrow (HE paraffin section); B. Fiber splitting \uparrow (MAT cryosection)

Diagnosis of Limb girdle muscular dystrophy was made based on history, proximal muscle weakness, creatine kinase levels, EMG, muscle biopsy and genetic studies. According to Jain foundation Automated LGMD diagnostic assistant (ALDA), Patient has medium probability and concordance of LGMD

subtypes LGMD2G (36.90) and LGMD2I (23.92) and medium low probability and concordance of LGMD2A (14.58). Genetic study confirmed LGMD2G.

Discussion

Due to heterogeneity and lack of diagnostic specificity, few reports are available on the prevalence of LGMD. Prevalence estimates range from 1 in 14,500 to 1 in 123,000 individuals [7,8]. According to one estimate by Fanin *et al.* (1997), carrier frequency can be estimated at 1:211; while Hackman *et al.* (2005) estimated the carrier frequency of sarglycanopathy at 1:150 [9].

Respiratory insufficiency may occur due to diaphragmatic weakness and cardiomyopathy and conduction abnormalities in heart in about 10%. Systemic classification is based on autosomal dominant (LGMD 1) and autosomal recessive (LGMD 2) inheritance. Fanin *et al.* [10] reported that males with LGMD may be clinically more severely affected than females, although mechanism is not known. Differential diagnosis include adult variant of spinal muscular atrophy (SMA III, Kugelberg-Welander disease), endocrine and acquired metabolic myopathies, polymyositis, dermatomyositis, other muscular dystrophies e.g., facio-scapulo-humeral, Becker, Duchenne muscular dystrophy, Type II Glycogen Storage Disease (Pompe Disease). Genetic studies are very specific for diagnosis but, very little information is available on the genetics of sarglycanopathies in India.

Our patient had no complaints of pain but showed cardiac involvement and conduction abnormalities. Patient was advised physiotherapy and ambulatory aids. Patient was advised for cardiac evaluation every 6 months. According to ALDA probability of LGMD2G was found which was confirmed by genetic studies. Gluteal and thigh atrophy may be prominent in this subtype which is present in our patient [11]. Calf hypertrophy occurs in about 50%, but some patients have calf atrophy that may resemble Miyoshi myopathy (LGMD2B). Cardiomyopathy occurs in about 50%.

Moreira *et al.* (1997) reported a family of Italian ancestry in which several members were affected with a unique form of limb-girdle muscular dystrophy which was later identified to be LGMD2G [12]. The parents (unaffected) had a total of 8 children, of whom 6 were affected. Mean age at onset was noted to be 12.5 years, and they showed difficulty with walking, running, climbing stairs and were unable to perform ankle dorsiflexion. Difficulty with walking on the heels appeared first before difficulty with walking on toes. Extraocular and facial muscles were spared in all patients. Although neck muscles were only very mildly affected or not affected, proximal muscle atrophy was marked in the upper limbs and both proximal and distal muscle atrophy was markedly seen in the lower limbs.

Moreira *et al.* (2000) [13] reported 2 additional affected families. In 9 affected patients from a new family and the family reported by Moreira *et al.* (1997), the age at onset ranged between 9 to 15 years, marked weakness in the distal muscles of the legs and proximal involvement was observed. Of 9 patients, 5 lost the ability to walk in their 3rd or 4th decade, and the remaining 4 were capable of walking at ages 22 to 44 years. Their serum creatine kinase levels were slightly increased, and rimmed vacuoles were noted in muscle biopsies. Heart involvement was observed in 3 of 6 affected members of 1 family. In a 3rd family, age at onset, typically characterized by difficulty in walking and climbing stairs, ranged from 2 to 15 years. All of the affected patients had pronounced calf hypertrophy (1 asymmetric), and their CK levels were increased 10- to 30-fold. The findings indicated phenotypic heterogeneity.

In affected members of the LGMD2G family reported by Moreira *et al.* (1997), Moreira *et al.* (2000) identified compound heterozygosity for 2 mutations in TCAP gene (604488.0001; 604488.0002). Affected members from 2 additional LGMD2G families had homozygosity for a TCAP mutation (604488.0001).

There are few other reports of on the functional role of ryanodine (RyR) receptors in muscular dystrophies and arrhythmias [14-16].

Conclusion

LGMD Onset, progression, pattern of symptoms, weakness and wasting vary among individuals and genetic subtypes. Cardiac conduction abnormalities can occur even in young patients with LGMD. Cardiac abnormalities in LGMD2G subtype are rarely reported. Diagnostic criteria are evolving but genetic information is lacking in India and other developing countries. Genetic studies are to be made available at affordable costs. More diagnostic analysis tools like ADLA should be made available for increasing probability of diagnosis and avoiding testing for all subtypes. Management should be tailored to the needs of the individual and subtype.

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