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CASE REPORT

Limb Girdle Muscular Dystrophy Type 2E (Beta-Sarcoglycanopathy): A Case Report

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Introduction

Limb girdle muscular dystophies(LGMDs) are a diverse collection of progressive, genetically defined illnesses of skeletal muscle.[1] All limb girdle muscular dystrophies (LGMD) are characterized by the gradual development of proximal weakness and tends to deteriorate as time progresses.[2] The prevalence of LGMD ranges from approximately 1 in 14,500 to 1 in 123,000.[2]Certain kinds of LGMD exhibit autosomal dominant inheritance patterns, whereas others manifest autosomal recessive inheritance patterns.

Autosomal recessive LGMD results from genetic abnormalities in the sarcoglycan complex. This complex is connected to the intracellular dystrophin protein via dystroglycan.Truncating and missense mutations in the β-sarcoglycan gene located in chromosome 4q12 causes primary β-sarcoglycan deficiency. It is a transmembrane glycoprotein that forms part of the sarcoglycan complex, deficiency of which causes autosomal recessive LGMD type 2E (LGMD 2E).[3]

Limb-Girdle Muscular Dystrophy (LGMD) favors hip, thigh, shoulder, and upper arm muscles. A typical LGMD Type 2E patient shows calf hypertrophy and Gower sign.[4] Other muscular dystrophies, such as X-linked recessive DMD also have these traits. Thus, pedigree analysis is necessary to suspect autosomal recessive limb girdle muscular dystrophies and warrants for further genetic diagnosis, counseling and management. Keeping this in mind, A patient with genetically diagnosed LGMD Type 2E is presented in this case report.

Case Report

A 7 year old girl, 2nd issue of consanguineous parents presented with the complaints of difficulty in standing from sitting position and climbing stairs for 2 years. She was studying in class one with good academic performance. Her bowel and bladder habits were normal. There was no history of cough, dysphagia, nasal voice, drooling. Her birth history was uncomplicated and no significant past history of illness. One paternal cousin, a 20 years old male, died due to same type of illness at the age of 20 yrs. He was suspected of having DMD. His sister had also same type of illness for which she was confined to wheel chair. Their parents also had consanguineous marriage (Fig.1).

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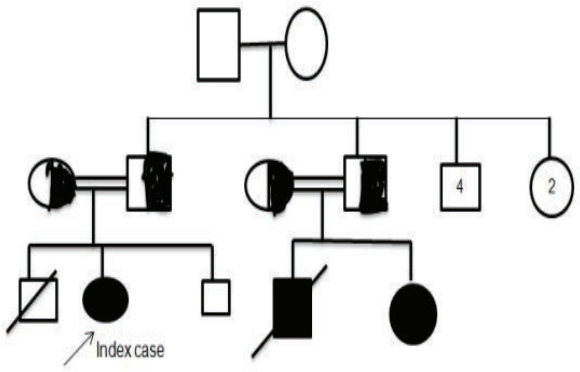

Fig.-1 *Three generation pedigree*

She had no apparent dysmorphism. Her vitals were normal. Her weight was 21 kg and heightwas117 cm and BMI 15.3 (falls just below 50thcentile). She was oriented to time, place and person. She had normal naming, repetition and comprehension. Cranial nerve examination revealed normal findings. She had increased bulk of midcalf muscle (calf hypertrophy) (Fig.-2) no wasting of thigh muscle, tone was normal, power 4/5 and normal deep tendonwith bilateral plantar flexor responses. Wadding gait was present and Gower sign positive.

Her investigation revealed CPK 8248U/L, EMG shows early recruitment, small -amplitude narrow duration polyphasic motor unit potential suggestive of muscular dystrophy. Whole exome sequencing shows pathogenic mutation of SGCB gene which is found to be associated with Limb girdle muscular dystrophy type 2E (Table I). Chest X ray, ECG, Echo-cardiography and Spirometry were normal.

Fig.-2 *Calf muscle hypertrophy*

The history, clinical examination and investigations confirmed limb girdle muscular dystrophy type 2 E. Counseling was done regarding the disease process, prognosisand management options. Genetic counseling was done regarding carrier detection and antenatal diagnostic approach for next pregnancy. Oral Steroid (deflazacort), vitamin D and calcium supplement was prescribed and physical therapy was provided to prevent contracture. We have further planned for autologous stem cell transplantation for this child at BSH&I.

Table I

Whole exome sequencing of the patient

Gene Chr	Transcript Id	Variant coordinate (GRCh38)	Variant type Zygosity	Variant Information	Classification As per ACMG Guideline
SGCB 4	NM_00232 Exon 1	52038225 Novel	Spllce donor Variant* Homozygous	c.33+2DC	Pathogenic

Discussion

Limb-girdle muscular dystrophy (LGMD) refers to non-X-linked, noncongenital muscular dystrophies with varying onset ages.[2] More than one disorder make up LGMD. From late in the first decade to the fourth decade, both male and female are affected. LGMDs cause weakness and wasting of muscles in legs and arms. Weakness of the diaphragm may cause respiratory insufficiency. Cardiomyopathy may also occur.[1] Unlike Duchenne muscular dystrophy, there appears to be no cognitive involvement in patients with sarcoglycanopathies. Based on inheritance, LGMDs are categorized into autosomal recessive and autosomal dominant, with multiple forms in each category. There are eight (10%) autosomal dominant (AD) and 26 (90%) autosomal recessive types.[2] Differential diagnosis include adult variant of spinal muscular atrophy (SMA III, Kugelberg-Welander disease), polymyositis, dermatomyositis, other musculardystrophies e.g., facio-scapulo-humeral, Becker, Duchenne muscular dystrophy, endocrine and acquired metabolic myopathies (e.g., Cushing's disease, hyper-thyroidism, steroid, and statin adminis-tration).[1]Reports on LGMDs and their subtypes are very few from Bangladesh.[5]

Sarcoglycan complex genetic abnormalities cause autosomal recessive LGMD muscular dystrophies. This complex is connected to intracellular dystrophin by dystroglycan.Mutation screening reliably detects sarcoglycan gene mutations. Muscle biopsy immunohistochemistry staining patterns may also indicate these mutations. The beta-sarcoglycan gene anomalies caused 62% of muscle biopsies to lack all four sarcoglycans (a-, b-, c-, d-).[3] The clinical features of primary â-sarcoglycan deficiency are early onset of proximal weakness, progression with loss of independent ambulation in the second decade, and elevated creatine kinase 3-22 times normal.[6-8]

Any condition that is associated with proximal muscle weakness involving pelvic girdle or lower extremity, can present with positive Gowers sign. such asDuchene muscular dystrophy, Limb-girdle and other muscular dystrophies, Proximal ascending pseudomyopathic diseases, Spinal muscular atrophy, Polymyositis, Discitis and Juvenile idiopathic arthritis.[9] Muscle diseases such as dystrophinopathies, limb-girdle muscular dystrophies, metabolic myopathy, parasite muscle pathologies, amyloid and sarcoid myopathy, dystrophic and non-dystrophic myotonias, endocrine disorders, and granulomatous myositis are among the causes of pseudohypertrophy.[10] Charcot-Marie-Tooth disease, spinal muscular atrophy, poliomyelitis, and radiculopathy are examples of neurological causes of pseudohypertrophy.[10] In our case, as we see in figure 1, the pedigree shows the male cousin of the patient who died was diagnosed as DMD patient probably due to positive Gower sign and pseudohypertrophy of calf muscle as genetic diagnosis was not established. But if the consanguinity of the parents could be kept in mind, Autosomal recessive LGMD comes as provisional diagnosis.

Previously when electroclinical and molecular diagnosis was not readily available, Serum CPK and muscle biopsy were the way to diagnose muscular dystrophy in general. Muscular dystrophies begin with CPK levels 50-300 times higher than usual although they decrease as muscle mass declines. Muscle biopsies show scattered necrotic and regenerating fibers and increased endomysial and perimysial connective tissue.can .But, based just on histological and histochemical evidence, it is challenging to diagnose a specific muscular dystrophy.[11] To determine the loss or insufficiency of sarcolemmal membrane-associated proteins, immunohistochemistry (IHC) analysis is necessary for a conclusive diagnosis. At present, when evaluating muscle biopsies from patients with a high clinical suspicion of MD but no genetic mutation has been found, this approach is very crucial.[12]

EMG shows early recruitment and the typical small-amplitude, narrow-duration, polyphasic motor-unit potentials that are seen in muscular diseases. Abnormal spontaneous activity in the form of fibrillations and positive sharp waves is not prominent but has been described in a few cases of LGMD. When present, it should raise the clinician's suspicion for an inflammatory myopathy, such as polymyositis. Our patient shows typical muscular dystrophy pattern.

Whole exome sequencing or Clinical exome sequencing under muscular dystrophy panel plays a crucial role for not only diagnosing but also pin pointing the specific subtype of muscular dystrophy. In a study by Ghaoui et al[13] pathogenic mutations in known myopathy genes were found in 45% of 60 families that completed full exome

sequencing. Interestingly, half of the genes were not LGMD genes, indicating clinical overlap between LGMD and other myopathies. Collagen, metabolic, and congenital myopathy genes caused phenotypic overlap.So it is better to perform whole exome sequencing to rule out other myopathies and also to identify novel pathogenic mutation.

About 30% of patients with sarcoglycanopathy had aberrant findings on electrocardiography or echocardiography, indicating dilated cardiomyopathy, according to Melacini et al[14] (1999). In addition, Raquel et al[15] showed FVC was low which is predictive of restrictive respiratory insufficiency in 74.2% of patients in their study with 100 patients with sarcoglycanopathies at long term follow up. So cardiac and respiratory evaluation and further follow up is necessary for LGMD type 2E. These investigations turned up normal results for our patient up until this point.

Physical and occupational therapy should be recommended for most patients to prevent contractures and maximize limb usage. Muscle cramps can be treated with baclofen, tizanidine, or gabapentin.[5,16] Role of steroid has been proven to decrease inflammation and it may influence the repair of weakened muscle cell membranes. an open label, exploratory single center study of once-weekly prednisone at 0.75-1 mg/Kg for 24 weeks showed some improvement in muscle performance and reduced serum CPK level.[17]

LGMD Type 2E entail respiratory involvement, particularly in patients with significant peripheral weakness.Pulmonary function tests can detect respiratory weakness. Noninvasive or invasive breathing technologies are beneficial in therapeutic settings. For patients with cardiac involvement(though less frequent in LGMD type 2E) serial ECG and echocardiograms are essential for monitoring heart state. Management of cardiomyopathy requires regular cardiologic follow-up and insertion ofintracardiac pacemakers or defibrillators asneeded.[16] SRP-9003 (bidridistrogenexeboparvovec) is an investigational gene therapy that uses the AAVrh74 vector, which is designed to be systemically and robustly delivered to skeletal, diaphragm and cardiac muscle, making it an ideal candidate to treat peripheral neuromuscular diseases. The 1st patient with LGMD type 2E started getting gene therapy under a phase 1 study since February 17, 2023 provided by Sarepta Therapeutics.[18]

With LGMD type 2E, life expectancy reaches adulthood and is dependent on the diagnosis and management of related heart and breathing muscle dysfunction.

Conclusion

Pseudohypertrophy of calf muscle with positive Gower sign are often present in muscular dystrophies other than DMD. Muscle biopsy without biochemical testing will not confirm the type of muscular dystrophy. Paediatricians should construct at least a three generation pedigree to identify the inheritence pattern and opt for making further genetic diagnosis which are vital for diagnosis of such rare disease like LGMD type 2E leading to further counselling and management**.**

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