Chapter 11
A 28-Year-Old Woman with Proximal Limb Weakness and Scapular Winging

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History

A 28-year-old woman presented with a few years of progressive weakness. An avid athlete, she played softball in college but developed exercise fatigue and dyspnea on exertion. She had constant leg soreness that got worse post exercise. Over time, she developed difficulty going upstairs, carrying groceries, and picking up her nieces and nephews. She did not have dysphagia, diplopia, or ptosis. Her fraternal twin sister carried a clinical diagnosis of limb girdle muscular dystrophy of unknown type, but her parents and grandparents did not have limb weakness.

Physical Examination

Her general examination was unremarkable. On strength testing, she had symmetric proximal limb muscle weakness and mild scapular winging. Hip adductors were weaker than abductors. There was no facial weakness.

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Investigations

CK level was mildly elevated 493 U/L (normal: < 200). ANA was negative. TSH and free T4 were normal. AST and ALT were mildly elevated but GGT was normal. She was initially evaluated by rheumatology, and NCS/EMG was not requested. MRI of the thighs showed moderate to severe atrophy and fatty infiltration of the hamstrings, adductor muscles, and gluteal muscles. A left quadriceps muscle biopsy was ordered.

Muscle Biopsy Findings

The left quadriceps muscle biopsy (Fig. 11.1) revealed mild chronic active myopathy with intact expression of dystrophin, alpha-sarcoglycan, alpha-dystroglycan, caveolin-3, dysferlin, and emerin. Immunostain for MHC Class I showed no abnormal myofiber upregulation.

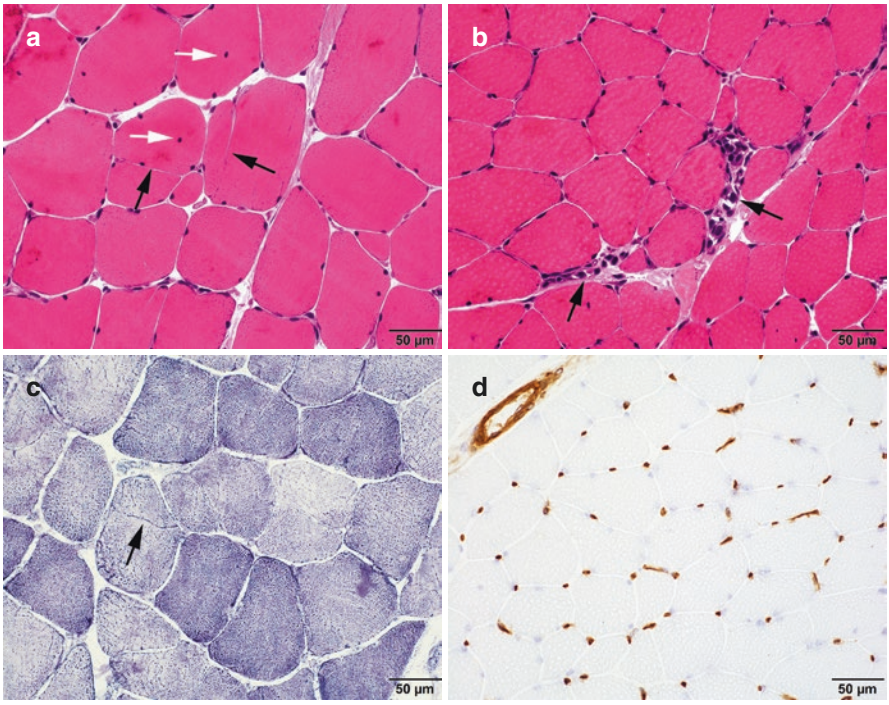

Fig. 11.1 Quadriceps muscle biopsy shows mild chronic active myopathy. (**a**), Chronic features include marked fiber size variation, split fibers (black arrows) and frequent internalized nuclei (white arrows). (**b**), Active features include occasional necrotic fibers (arrows) and absence of regenerating fibers. (**c**), NADH-TR stain highlights split fibers (arrow). No lobulated myofibers are seen in this biopsy. (**d**), MHC I stain shows a normal capillary staining pattern, there is no abnormal myofiber reactivity

Additional Investigation After Muscle Biopsy Diagnosis

The patient was referred to our neuromuscular clinic after obtaining the muscle biopsy diagnosis. Based on her history, family history, MRI, and muscle biopsy findings, a limb-girdle muscular dystrophy (LGMD) was suspected. Subsequent genetic testing revealed two variants in the *CAPN3* gene: c.1468C > T (p.R490W) and c.1063C > T (p.R355W), both of which have been reported as pathogenic mutations [1, 2].

Final Diagnosis

Limb girdle muscular dystrophy type 2A (LGMD2A).

Patient Follow-up

Patient underwent physical therapy for balance training and started using a cane for safe ambulation. At follow up, she complained of daily bouts of coughing, worse with lying flat. Transthoracic echocardiogram was normal. Spirometry showed FVC 89% predicted, MIP 54% predicted, and MEP 84% predicted. She was diagnosed with mild restrictive lung disease. One year after diagnosis, she gave birth to her first child without obstetric complication.

Discussion

The limb girdle muscular dystrophies (LGMD) are genetically heterogeneous, autosomally inherited, have a childhood to adult onset, and are characterized by progressive muscle weakness and wasting of the shoulder- and pelvic-girdle muscles [3]. LGMD is the fourth most common form of muscular dystrophy, with a prevalence of 1.63 per 100, 000 [4]. Autosomal dominant subtypes are denoted as LGMD1 and autosomal recessive subtypes are denoted as LGMD2. There are many subtypes of LGMD: 26 LGMD2 and 8 LGMD1. In general, LGMD2 is more common than LGMD1.

LGMD2A is most common in American and European countries, except in Denmark where LGMD2I is more common [3]. Its clinical presentation is variable with a wide range in onset from childhood to adulthood, but teenage onset is typical. Muscle weakness can start in the pelvic girdle (Leyden-Mobius variant) or the shoulder girdle (Erb variant). Young patients can present with asymptomatic hyperCKemia or transient eosinophilic myositis [5]. Characteristic features include toe walking in early childhood, scapular winging, scoliosis, axial muscle weakness, joint contractures (especially of the Achilles tendon), and sparing of the facial

muscles. The hamstrings, gluteal muscles, and hip adductors are often weak and atrophic. Cardiac function is distinctly normal. As the illness progresses over decades, ambulation is impaired and nearly half the patients become wheelchair dependent. Respiratory complication can be seen in some patients, but is not a salient feature of LGMD2A. There is some gender variability with women having less weakness compared to men [6].

LGMD2A is caused by mutations in the *CAPN3* gene found on chromosome 15, which encodes for calpain-3 [5]. Calpain-3 is a muscle specific protein involved in sarcomere remodeling. Though its exact function is unknown, calpain-3 helps target actin and myosin for proteasomal degradation via ubiquitination. It is highly active in both muscle catabolism and anabolism [7].

The differential diagnosis for LGMD2A is broad. It is often hard to clinically distinguish LGMD2A from other forms of autosomal recessive LGMD such as LGMD2B (dysferlinopathy), LGMD2C-2F (sarcoglycanopathies), LGMD2G (telethoninopathy), and LGMD2J (titinopathy), thereby necessitating a muscle biopsy and/or genetic analysis. Duchenne and Becker muscular dystrophy also have a clinical presentation identical to LGMD2A, but these disorders have prominent cardiac involvement and inheritance pattern is X-linked recessive. Emery-Dreifuss muscular dystrophy presents with joint contractures similar to LGMD2A, but cardiac involvement is more conspicuous. Facioscapulohumeral muscular dystrophy also presents with progressive proximal shoulder girdle weakness, but prominent facial weakness and autosomal dominant inheritance should distinguish this from LGMD2A. LGMD2A can also be confused for metabolic myopathy given exercise intolerance and myalgia. However, most cases of metabolic myopathy can be readily distinguished from limb girdle muscular dystrophy by muscle biopsy.

Serum CK is elevated 5-80× normal in LGMD2A and needle electromyography shows a myopathic pattern. Genetic testing confirms the diagnosis; however, it is not uncommon to detect variants of unknown significance in which case a muscle biopsy should be performed [5]. Since limb girdle muscular dystrophy is phenotypically diverse, a multigene panel is preferred over single gene testing. The 24 coding exons of *CAPN3* can be directly sequenced by next-generation exome sequencing whereas intron mutations can be identified by analysis of complementary DNA (cDNA) [5, 8, 9].

MRI may be a valuable tool for preliminary screening of LGMD2A and can enhance the efficiency of muscle biopsy and DNA analysis. MRI shows a characteristic pattern of muscle involvement: severe fatty infiltration in the long head of biceps femoris, semimembranosus, semitendinosus, and adductor muscles [6, 10] as seen in our patient.

Muscle biopsy can aid in diagnosis by confirming dystrophic changes in muscle and excluding other disease processes such as metabolic myopathies, immune mediated myopathies, or neurogenic etiologies. The hallmarks of dystrophic changes are chronic active myopathic changes with ongoing myofiber necrosis in a

background of endomysial fibrosis and fatty replacement. Other less specific chronic changes include marked fiber size variation with presence of hypertrophic fibers, split fibers, and frequent internalized nuclei. These changes are reflective of the time course of the disease process rather than any particular disease. It is usually not possible to specifically classify a muscular dystrophy based on histology or enzyme histochemistry alone. Two helpful features have been reported in association with LGMD2A, including (1) markedly reduced regenerating fibers compared to other muscular dystrophies [5] and (2) eosinophilic myositis in childhood [11]. Definitive diagnosis requires protein and/or genetic analysis. Immunohistochemistry is helpful only in instances of total protein loss; mutations that cause partial loss of calpain-3 cannot be readily detected by this method. Immunoblot analysis is able to capture partial protein loss. However, immunoblot misses 20–30% of LGMD2A cases which have a mutation that impairs the function of the protein rather than its quantity [5]. A functional assay that detects loss of the normal autocatalytic activity of the protein can identify some but not all of the functional mutations. Genetic testing in the form of LGMD panel is becoming the principle method for confirming the diagnosis.

To date, there is no specific treatment for any of the LGMD subtypes. Once diagnosis is made, treatment for the condition is generally supportive. Physical therapy and orthotic intervention is important to maintain safe ambulation and independence for as long as possible. Passive range of motion promotes mobility and flexibility. Gentle and low impact aerobic exercise improves cardiovascular performance and reduces fatigue. Surgical correction of foot deformities, scoliosis, and contractures might be useful [12]. Given the risk of respiratory involvement, regular assessment of forced vital capacity and overnight pulse oximetry are very important [12, 13]. Non-invasive ventilation and cough assist devices may be needed in select individuals [14]. Finally, genetic counseling is important in family planning.

Pearls

Clinical Pearls

1. LGMD2A characteristically causes selective weakness and atrophy of the hamstrings, gluteal muscles, and hip adductors. Scapular weakness and joint contractures are other common features.
2. Muscles of the heart and face are spared in LGMD2A.
3. MRI of the thigh detects fatty infiltration in the adductors and hamstrings and can be used as a screening tool.
4. Mutation testing for LGMD2A can be done by next generation sequencing of the 24 coding exons of the *CAPN3* gene.

Pathology Pearls

1. The degree of pathology varies greatly and does not necessarily correlate with clinical severity.
2. A chronic active myopathy that lacks regenerating fibers, and eosinophilic myositis in children are relatively specific features of LGMD2A.
3. Although lobulated myopathy has often been associated with LGMD2A, it is neither sensitive nor specific. Lobulated myopathy can be seen in a variety of hereditary and non-hereditary conditions [15].
4. In muscle with chronic active myopathy, MHC class I immunostain is helpful in differentiating muscular dystrophies (usually negative) from inflammatory myopathies (usually positive). However, notable exceptions exist both ways. For example, dysferlinopathy (LGMD2B) and facioscapulohumeral dystrophy (FSHD) may have prominent inflammation and myofiber MHC1 upregulation. Conversely, inflammatory myopathies undergoing long-term steroid treatment may have negative MHC1 myofiber expression.

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