Case 38
A Common Cause of Progressive Proximal Weakness…

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History

A 34 year old woman presented with a history of gradually progressive proximal lower limb weakness. She was the product of a normal full term delivery, achieved normal motor milestones and was very good at school sports. Her husband noticed mild difficulty climbing stairs from when she was 17. The patient first noticed symptoms at age 28 of difficulty getting up from the floor. Her symptoms progressed gradually with increasing difficulty walking long distances. She had no symptoms related to the cranial nerves or upper limbs.

There was no family history of neuromuscular disease including two siblings and three children. There was no parental consanguinity. There was no past medical history and she took no regular medications.

Examination

General and cardio-respiratory examination were normal. She walked with a waddling gait. Cranial nerve examination was normal including facial muscle power. There was no scapula winging or scoliosis. There was mild symmetrical

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weakness of shoulder abduction (MRC grade 5−/5) with mild weakness of hip flexion (MRC grade 4/5) and knee flexion (MRC grade 4+/5). Her distal muscle power, muscle bulk, reflexes, co-ordination and sensation were normal.

Investigations

Her creatine kinase (CK) was significantly elevated at 1891 IU/L (26−140). Her nerve conduction studies were normal and electromyography demonstrated myopathic motor units in her proximal muscles. Quadriceps muscle biopsy was performed and showed dystrophic features (Fig. 38.1). A lower limb MRI demonstrated fatty replacement of muscle particularly in the posterior thigh (Fig. 38.2). Echocardiogram showed mildly dilated left ventricle (LVEDD 5.5 cm) but normal systolic function. *FKRP* gene analysis demonstrated homozygous mutations c.826C >A (p.Leu276Ile).

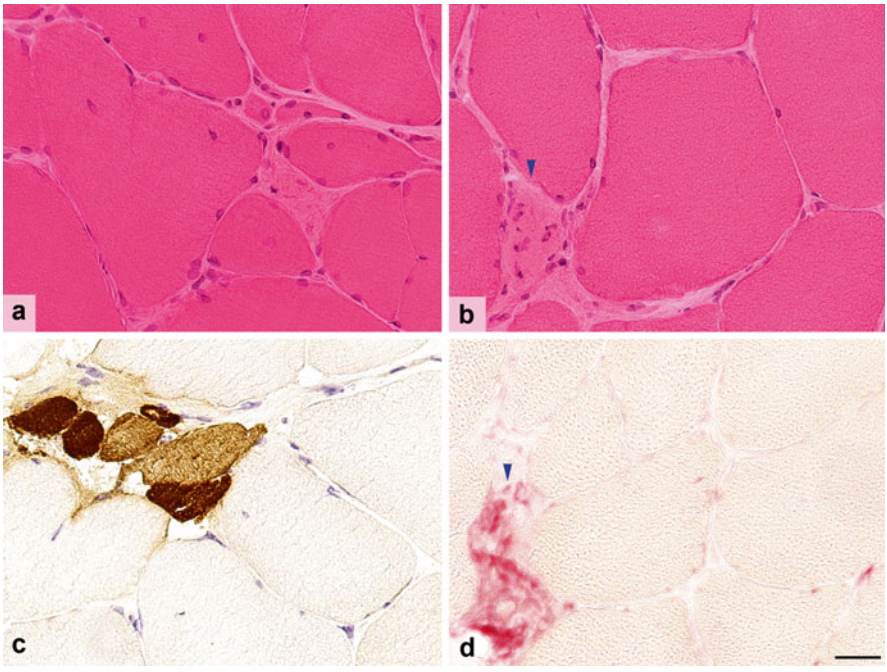

Fig. 38.1 Muscle biopsy of Limb Girdle Muscular Dystrophy type2I. Haematoxylin-Eosin stained sections (**a, b**) show marked variation in fibre size and occasional necrotic fibres (*blue arrowhead* in **b**). Immunostaining for neonatal myosin (**c**) reveals frequent positively labelled fibres. Histochemical staining for acid phosphatase (**d**) accentuates a necrotic fibre overrun by macrophages (*blue arrowhead*). Scale bar: 30 μm (Image courtesy of Zane Jaunmuktane and Sebastian Brandner)

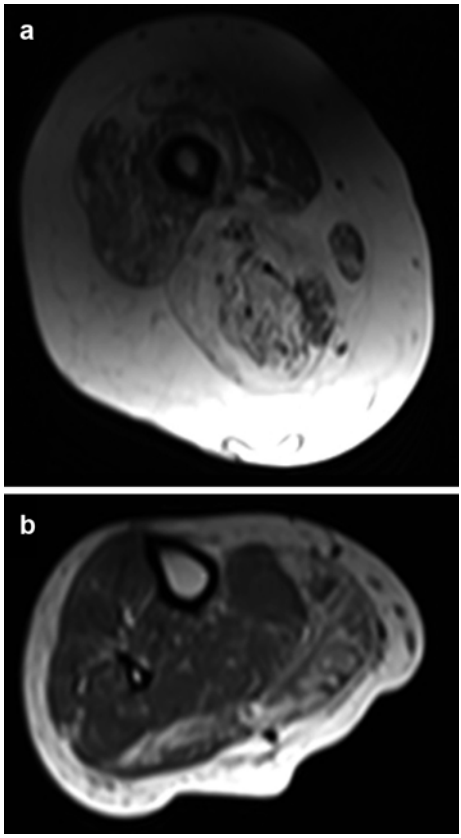

Fig. 38.2 Lower limb MRI: Transverse T1 weighted images through the right thigh (**a**) and calf (**b**). In the thigh fatty infiltration is greater in the posterior than anterior compartment with greatest involvement of biceps femoris. The calf is less affected with mild fatty infiltration of medial and lateral gastrocnemius

Diagnosis

Limb Girdle Muscular Dystrophy Type 2I: FKRP homozygous mutations c.826C >A (p.Leu276Ile).

Discussion

The clinical history is consistent with a myopathic process with proximal weakness, no upper motor neuron signs, normal sensation and intact reflexes. The gradually progressive time-course suggested a degenerative cause which was probably genetic. The clinical diagnosis of a limb girdle muscular dystrophy (LGMD) was supported by a raised CK, a myopathic EMG and a dystrophic muscle biopsy. FKRP is the commonest cause of LGMD in Northern Europe and was an appropriate initial genetic test. Genetic diagnosis is important as it enables genetic counselling for

offspring and other family members, appropriate screening of potential other organ involvement, such as cardiomyopathy, more specific prognostic advice and ultimately, potential future molecular therapy.

LGMDs are classified according to inheritance pattern, with LGMD Type 1 autosomal dominant and LGMD Type 2 autosomal recessive. LGMD are sub-classified according to the responsible gene which currently includes LGMD1A-H for the dominant cases and LGMD2A-S for the recessive cases. There are likely to be further genetic causes for LGMD discovered in the future as many cases remained genetically undefined. The most likely clinical diagnosis can sometimes be narrowed down by clinical features, CK level, muscle biopsy findings, and MRI pattern. A LGMD "genetic panel" using next generation sequencing technology will probably replace the requirement for a muscle biopsy in the near future.

LGMD2I is caused by mutations in the gene encoding Fukutin Related Protein (FKRP) which has a role in glycosylation of alpha-dystroglycan. It is one of a group of disorders associated with abnormal alpha-dystroglycan labelling on muscle biopsy. The other disorders associated with abnormal alpha-dystroglycan usually present with a congenital myopathy and occasionally FKRP-related disease may present at birth. Specific clinical clues to LGMD2I include calf hypertrophy, cardiac and respiratory muscle involvement, and very high CK levels. A specific pattern of muscle involvement may also seen on MRI (Fig. 38.2). LGMD2I is one of the most common forms of LGMD in Northern Europe, with a common mutation (C826A) accounting for more than 90 % of cases. It is therefore reasonable, in a patient with the appropriate genetic background and clinical phenotype, for this specific mutation to be analysed at an early point in the diagnostic workup.

References

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