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Case Report

Myofibrillar Myopathy Mimicking Polyneuropathy

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Abstract
A 76-year-old man with a 5-year history of gait difficulties was suspected to have length-dependent sensorimotor polyneuropathy. Electrodiagnostic results pointed to a foot drop of neurogenic etiology, except for the prominence of myotonic discharges on needle EMG. Tests for acquired and genetic causes of polyneuropathy were unrevealing. The patient's first-degree cousin, with a much different clinical phenotype had been diagnosed with myofibrillar myopathy. Our patient was eventually found to carry the same myotilin c.179C>T p.Ser60Phe mutation. Muscle MRI was helpful in delineating clinically unsuspected involvement of paraspinal and pelvi-femoral muscles, as well as showing marked myopathic fatty infiltration of distal leg muscles. The association of neuropathy and myopathy is a recognized feature of myofibrillar myopathy. In some patients with unexplained foot drop, whole-body muscle MRI and a dedicated genetic mutation testing strategy may help reveal a diagnosis of genetic myopathy.

Introduction

The term limb girdle muscular dystrophy (LGMD) was initially coined to describe genetic myopathies with prominent involvement of the shoulder and hip girdle musculature, and to

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distinguish these from the more common X-linked dystrophinopathies (Duchenne and Becker muscular dystrophy). As a result of advances in molecular genetics, the LGMD classification is now based on the identification of mutations of genes associated with specific proteins of the sarcolemma, cytosol, or nucleus [1]. The range of phenotypic expression may include not only a classical girdle myopathy but also distal or oculofacial myopathy, as well as additional distinct features such as cardiomyopathy, cardiac arrhythmia, scapular winging, contractures, rigid spine, distal limb myopathy, calf hypertrophy, myotonia, muscle rippling, highly variable CK elevation, and polyneuropathy [2]. Within and between kinships carrying the same pathogenic point mutation, disease expression can be highly variable. This case report documents a patient with myofibrillar myopathy (previously categorized as LGMD1A [3]) where the clinical and electrodiagnostic presentation was primarily suggestive of length-dependent axonal polyneuropathy, leading to an erroneous initial suspicion of acquired neuropathy or CMT2.

Case Presentation

A 76-year-old man was referred to our neuromuscular clinic for a 5-year history of insidiously progressive leg weakness. He had noticed an increasing tendency to slap his right foot on the ground and trip on uneven surfaces. He subsequently noticed evident increasing bilateral foot drop. There was also a more global tiredness in both lower limbs with long duration exertion, and mild difficulty going up stairs or rising from a low chair. There was no impairment in the bulbar territory or the upper limbs. In parallel, he complained of sensory loss in both feet up to the mid-shin level, associated with mild superficial dysesthesia.

A previous assessment in a different clinic had concluded he may have bilateral L5 radiculopathy, though MRI of the lumbar spine was unrevealing.

On examination, there was no significant muscular atrophy. Isometric manual muscle strength testing showed weakness limited to the distal lower limbs in the following distribution: ankle dorsiflexion was MRC grade 2/5 on the right, 4–/5 on the left; ankle inversion and eversion were 4/5; ankle plantar flexion weakness was mostly revealed by difficulty standing on toes. Hip girdle and thigh compartment muscles were, however, graded 5/5. Sensory testing showed length-dependent sensory impairment for pinprick/pain and light touch (Fig. 1), with normal perception of vibration and proprioception. Myotatic reflexes were graded 1+ in the upper limbs, but absent bilaterally at the knees and ankles.

The following blood tests were normal or negative: CBC, vitamin B_{12}, TSH, serum protein electrophoresis, hemoglobin A1C, paraneoplastic antibodies, renal and liver function studies. The serum CK was mildly elevated at 508 U/L. A 30-gene next-generation sequencing panel for Charcot-Marie-Tooth disease was unrevealing. Because of the presence of myotonic potentials on EMG, genetic testing for myotonic dystrophy types 1 and 2 was also performed and was negative.

Nerve conduction studies showed mildly reduced peroneal and tibial compound muscle action potential amplitudes with normal distal motor latencies and conduction velocities. Upper and lower extremity sensory nerve conduction studies were within normal limits. Needle electromyography showed abnormal spontaneous activity (fibrillations, positive sharp waves) as well as polyphasic, long-duration motor unit potentials with decreased recruitment, most prominently in the tibialis anterior muscles, but to a lesser extent in the gastrocnemius muscles. Prominent myotonic discharges were also noted in several muscles. In contrast, the biceps brachii and vastus lateralis muscles were normal. These results overall were in keeping with a predominantly motor length-dependent polyneuropathy. The normal sensory

conduction studies, in the context of distal sensory symptoms and impaired pain and touch sensation on examination, suggested a restricted involvement of small/unmyelinated sensory fibers.

Two years after his initial assessment, the patient mentioned that a first-degree paternal cousin was diagnosed with LGMD1A/myofibrillary fibrillary myopathy. This cousin presented with a different phenotype, consisting predominantly of girdle-distribution proximal quadriparesis with marked CK elevation (1,000–10,000 U/L), EMG findings of widespread myotonic discharges with typical electrophysiologic hallmarks of myopathy, and only mild polyneuropathy. Our patient was thus tested for myotilin mutations found to have the same heterozygous gene variant as his cousin: *MYOT* c.179C>T p.Ser60Phe (MNG Laboratories, Atlanta, GA, USA). This variant is classified as type 1 pathogenic according to the ACMG guidelines.

Whole-body MRI was also subsequently performed on our patient, revealing prominent fatty infiltration in paraspinal and lower limb muscles, with a pattern felt to be typical for myofibrillar myopathy (Fig. 2).

Discussion

This patient illustrates some pitfalls in the diagnosis of genetic myopathy when there is weakness in a distal distribution. This clinical phenotype will commonly be first interpreted as suggestive of length-dependent acquired or genetic polyneuropathy. Selective calf weakness without sensory loss may be seen in distal muscular dystrophy, with a rich nosology including distal myopathy 3 (MPD3), hereditary inclusion body myopathy type 2 (IBM2), tibial distal myopathy, and the eponymic syndromes known as Laing, Udd, Welander, and Miyoshi distal myopathy [4]. The diagnostic challenge may be even more complex when there is a combination of genetic myopathy and polyneuropathy. The association of myopathy and neuropathy has been well documented in myotonic dystrophy type 1 and 2, several mitochondrial disorders, myofibrillar myopathy [5], laminin-α (merosin) congenital muscular dystrophy, and lamin A/C disorders [6].

In our patient, unequivocal deficits in pain and light touch perception pointed to a small fiber sensory polyneuropathy. There was sparing of large diameter myelinated sensory axons by clinical and electrodiagnostic criteria. Needle EMG showed a pattern most in keeping with a neurogenic disorder, though the relative prominence of myotonic discharges would raise a suspicion of myopathy. Myotonic discharges may occur to a minimal degree in the setting of active denervation but are more typical of channelopathies and dystrophic myotonias [7]. They have been described in a wide range of other myopathies, notably the inflammatory myopathies [8] and acid maltase deficiency [9]. They may also occur to be a characteristic feature of myofibrillar myopathies [10].

In retrospect, it is likely that the marked distal leg weakness of our patient, affecting more prominently ankle dorsiflexors than plantar flexors, was mostly myopathic. Indeed, with few exceptions, chronic neurogenic foot drop is expected to be associated with prominent denervation atrophy. The exception to this rule is the infrequent occurrence of neurogenic muscular hypertrophy, mostly described in chronic lumbosacral radiculopathy, spinal muscular atrophy, or neuromyotonia [11]. Muscle MRI in our patient showed very marked fatty infiltration with relative preservation of overall soft tissue circumference, which is more in keeping with muscular dystrophy. This case is a good example of the unique contribution of muscle MRI in the diagnosis of neuromuscular disease. MRI is expected to show increasing T1 signal intensity with fatty infiltration Increased T2 signal may correlate with the presence of muscle

edema [12]. In contrast, MRI shows characteristic patterns in acute/subacute denervation (low T1 signal, high signal on fluid-sensitive sequences). The sequence signal characteristics in chronic denervation may however be similar to that of muscular dystrophy [13].

Though our patient reported some decreased exercise tolerance in axial and girdle muscles, there was little evidence of proximal myopathy on bedside manual isometric muscle strength testing in the clinic. MRI allowed demonstration of definite fatty infiltration of paraspinal muscles, gluteal and lateral posterior thigh muscles, in addition to the clinically involved distal leg muscles. The muscle MRI pattern of fatty infiltration may thus help diagnose and discriminate between different forms of genetic myopathy [14]. For example, the muscles reported to be most affected in myofibrillar myopathy/LGMD1A are: gluteus medius more than maximus; adductor major, semimembranosus and biceps femoris more than semitendinosus; all calf muscles with relative sparing of peroneus muscles.

This case vividly demonstrates the need to consider a broad anatomical differential diagnosis in cases of apparent neurogenic calf paresis. If there are atypical clinical or EMG features, genetic studies and muscle MRI may help reveal distal myopathies that can mimic polyneuropathy.

Statement of Ethics

The subject of this case report gave written informed consent for this case report publication (including publication of images). This case report is approved by our institutional ethics review board.

Disclosure Statement

The authors (Drs. P.R. Bourque, A. Breiner, and J. Warman-Chardon) have no conflict of interest to declare.

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Author Contributions

Dr. Bourque: case selection, acquisition of photographs, initial manuscript draft, search of relevant references. Dr. Breiner: critical review of manuscript, selection and discussion of imaging. Dr. Warman-Chardon: critical review of manuscript, writing of discussion statements.

References

1 Vissing J. Limb girdle muscular dystrophies: classification, clinical spectrum and emerging therapies. Curr Opin Neurol. 2016 Oct;29(5):635–41.
2 Liewluck T, Milone M. Untangling the complexity of limb-girdle muscular dystrophies. Muscle Nerve. 2018 Aug;58(2):167–77.

3 Straub V, Murphy A, Udd B, Corrado A, Aymé S, Bönneman C, et al.; LGMD workshop study group. 229th ENMC international workshop: limb girdle muscular dystrophies - Nomenclature and reformed classification Naarden, the Netherlands, 17-19 March 2017. Neuromuscul Disord. 2018 Aug;28(8):702–10.
4 Udd B. Distal myopathies. Curr Neurol Neurosci Rep. 2014 Mar;14(3):434.
5 Claeys KG, Fardeau M. Myofibrillar myopathies. Handb Clin Neurol. 2013;113:1337–42.
6 Benedetti S, Bertini E, Iannaccone S, Angelini C, Trisciani M, Toniolo D, et al. Dominant LMNA mutations can cause combined muscular dystrophy and peripheral neuropathy. J Neurol Neurosurg Psychiatry. 2005 Jul;76(7):1019–21.
7 Quinn C, Salajegheh MK. Myotonic Disorders and Channelopathies. Semin Neurol. 2015 Aug;35(4):360–8.
8 Kazamel M, Sorenson EJ, Milone M. Clinical and Electrophysiological Findings in Hereditary Inclusion Body Myopathy Compared With Sporadic Inclusion Body Myositis. J Clin Neuromuscul Dis. 2016 Jun;17(4):190–6.
9 Kassardjian CD, Engel AG, Sorenson EJ. Electromyographic findings in 37 patients with adult-onset acid maltase deficiency. Muscle Nerve. 2015 May;51(5):759–61.
10 Hanisch F, Kraya T, Kornhuber M, Zierz S. Diagnostic impact of myotonic discharges in myofibrillar myopathies. Muscle Nerve. 2013 Jun;47(6):845–8.
11 Walters J. Muscle hypertrophy and pseudohypertrophy. Pract Neurol. 2017 Oct;17(5):369–79.
12 Diaz-Manera J, Llauger J, Gallardo E, Illa I. Muscle MRI in muscular dystrophies. Acta Myol. 2015;34(2-3):95-108.
13 Weber MA, Wolf M, Wattjes MP. Imaging Patterns of Muscle Atrophy. Semin Musculoskelet Radiol. 2018 Jul;22(3):299–306.
14 Jungbluth H. Myopathology in times of modern imaging. Neuropathol Appl Neurobiol. 2017 Feb;43(1):24–43.

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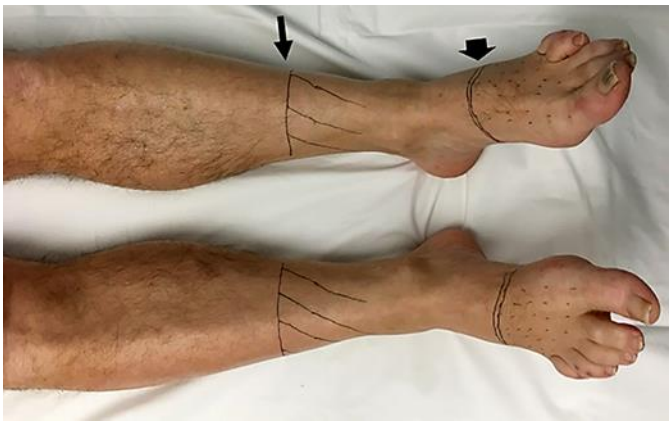

Fig. 1. Clinical photograph of lower limbs. Despite marked bilateral foot drop, there is no significant soft tissue atrophy, which would be atypical for chronic denervation. Two separate sensory levels are indicated for impairment of pinprick/pain (lower third of tibia, long arrow) and light touch (mid-foot, arrowhead).

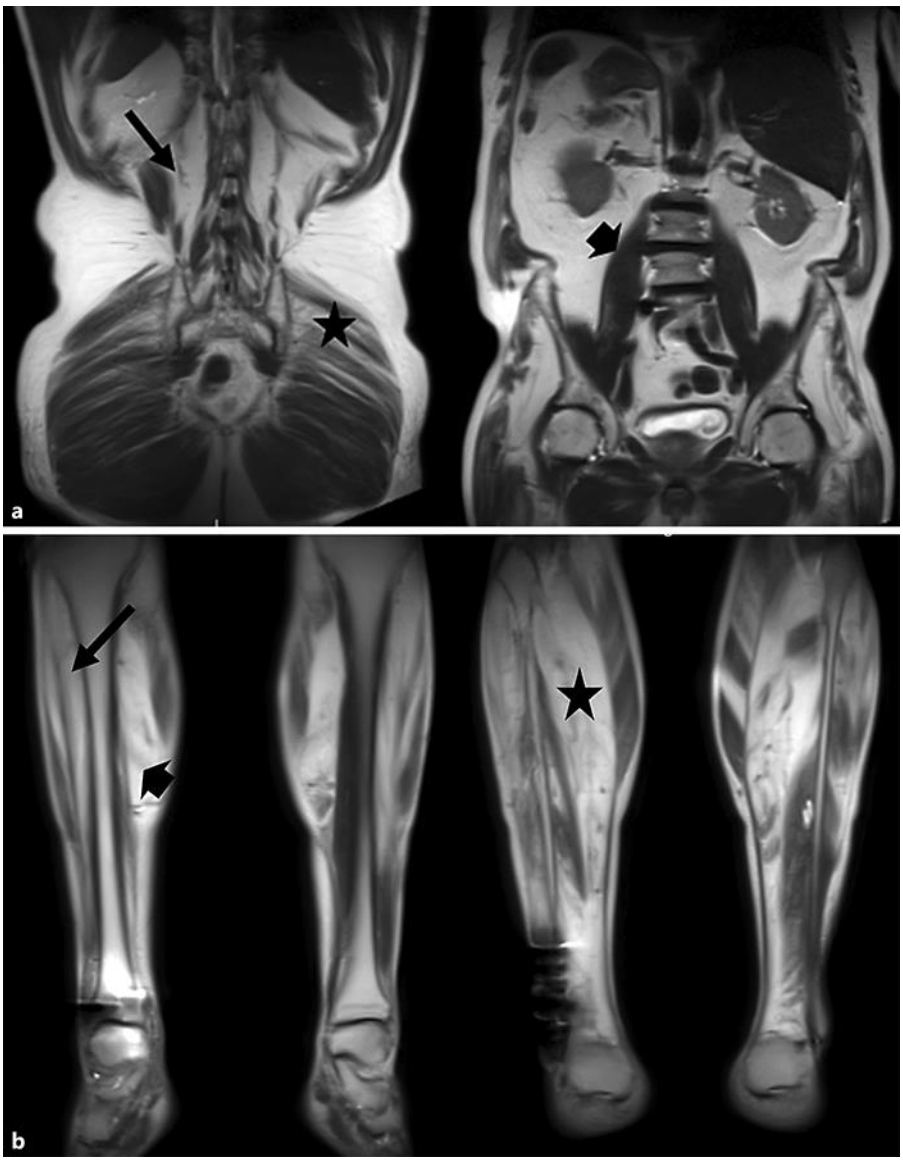

Fig. 2. Representative whole-body coronal MRI sections (TE: 87, TR: 2,000, FA: 150). **a** At the level of the trunk, there is marked fatty replacement of lumbar paraspinal muscles (long black arrow) whereas the psoas muscles are relatively spared (arrowhead). There is also moderate fatty streaking of the gluteus medius muscles (star), more prominently than in the gluteus maximus. **b** At two different anteroposterior levels of the calf, there is marked fatty replacement of the tibialis anterior (long black arrow), medial gastrocnemius (arrowhead), and soleus muscles (star).