Clinical Reasoning: A case of bilateral foot drop in a 74-year-old man

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Section 1

A 74-year-old man with no relevant medical history presented with 5 years of slowly progressive bilateral foot drop. He had used ankle foot orthoses for 3 years prior to presentation. There was no report of upper extremity weakness, numbness, paresthesia, myalgias, muscle cramps, or stiffness. He had attained age-appropriate developmental milestones as a child and was athletic, keeping up with his peers. His mother had bilateral foot drop, ankle contractures, and difficulty with ambulation. His brother, 2 daughters, and a son lacked similar symptoms. Neurologic examination showed bilateral distal lower extremity weakness (Medical Research Council grade 0/5 ankle dorsiflexion and eversion and grade 4/5 ankle plantar flexion and inversion), symmetric distal leg and intrinsic foot muscle wasting, absent patellar and Achilles tendon reflexes, and a steppage gait. Tone was reduced at bilateral ankles. Sensory examination including light touch, pinprick, vibration, and proprioception was intact. Mild bilateral pes cavus and hammertoes were noted. The remainder of the neurologic and physical examination was normal.

Questions for consideration:

1. What is the differential diagnosis?
2. What investigations should be considered?

GO TO SECTION 2

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Section 2

Foot drop is primarily caused by the weakness of the tibialis anterior muscle that produces ankle dorsiflexion. A systematic approach through anatomical localization is critical to determine the origin of foot drop. CNS disorders involving the brain or spinal cord uncommonly manifest with pure, bilateral foot drop. The tibialis anterior muscle is predominantly innervated by the L5 nerve root. Spinal cord lesions above L5 can cause bilateral foot drop. However, the absence of upper motor neuron signs or other features of spinal cord dysfunction in our patient argue against these. Anterior horn cell disorders also cause foot drop. Amyotrophic lateral sclerosis is unlikely due to the absence of upper motor neuron signs, fasciculations or bulbar involvement, and the very slow rate of progression. Progressive muscular atrophy that only affects lower motor neurons commonly presents with asymmetrical segmental involvement, though symmetrical involvement of distal muscles has been described.[1] Bilateral L5 radiculopathies or lumbosacral plexopathy may also cause bilateral foot drop. However, the absence of sensory symptoms, pain, or weakness in proximal L5 myotomes in our patient is atypical. Peripheral nerve lesions involving bilateral sciatic or peroneal (fibular) nerves that innervate the tibialis anterior muscles is a possibility. The peroneal nerves are susceptible to compression at the fibular head. Associated sensory involvement is typically seen. A lack of a history suggesting compression of the peroneal nerves, the absence of sensory symptoms or signs, and the associated ankle inversion and plantar flexion weakness (innervated by the tibial nerve) make compression at the fibular head an unlikely etiology. Similarly, the absence of sensory findings or hamstring weakness argue against a localization to the sciatic nerves. Polyneuropathy (hereditary or acquired) is also a common cause of foot drop. The pure motor clinical phenotype limits the range of possible peripheral neuropathies. Multifocal motor neuropathy may cause a chronic distally accentuated motor neuropathy and foot drop, but the symmetrical presentation and family history favor a distal hereditary motor neuropathy (dHMN). The most common form of distal hereditary polyneuropathy is Charcot-Marie-Tooth disease (CMT). CMT is a motor sensory polyneuropathy that by definition has sensory involvement and abnormal sensory nerve action potentials. However, the purely motor symptoms and family history in our

Table Electrodiagnostic (EMG–nerve conduction studies [NCS]) findings

Nerve	Stimulus	Recording site	Latency, ms	Amplitude (motor = mV, sensory = μV)	Conduction velocity, m/s
Motor NCS					
Left ulnar	Wrist	ADM	2.8	9.81	
	Below elbow	ADM	6.3	8.96	55.7
	Above elbow	ADM	8.2	7.38	52.6
Left tibial	Ankle	AH	6.6[a]	1.5[a]	
	Popliteal fossa	AH	14.9	0.38[a]	43.9
Sensory NCS					
Left ulnar	Wrist	Digit V–wrist	2.2	13	50
Left radial	Forearm	Forearm–snuff box	2	19.6	50
Left sural	Lower leg	Ankle–lower leg	3	5.0	40.2

	Spontaneous activity			Motor unit morphology			Interference pattern	
Muscle	**IA**	**Fibs/PW**	**Fasc**	**Duration**	**Amplitude**	**Phase**	**Activation**	**Recruitment**
Needle EMG examination								
FDI	Normal	0	0	Normal	Normal	None	Normal	Normal
VM	Normal	0	0	Slight increase[a]	Normal	None	Normal	Mildly reduced (−1)[a]
TA	Increased[a]	+2[a]	0	Normal	Normal	None	Normal	Severely reduced (−3)[a]
MG	Increased[a]	+1[a]	0	Normal	Normal	Slight increase[a]	Normal	Severely reduced (−3)[a]

Abbreviations: ADM = adductor digitorum minimi; AH = abductor hallucis; Fasc = fasciculation; FDI = first dorsal interosseous; Fibs = fibrillation potentials; IA = insertional activity; MG = medial gastrocnemius; PW = positive waves; TA = tibialis anterior; VM = vastus medius.
[a] Abnormal findings.

patient lead to a strong suspicion of dHMN, a subtype of hereditary neuropathy with clinical and genetic overlap with CMT. The cardinal feature of dHMN is a very slowly progressive length-dependent neuropathy often starting in the first 2 decades,[2] although later onset has been reported.[3] There are multiple genes associated with dHMN; however, a causative genetic defect can currently only be identified in fewer than 20% of patients. Bilateral foot drop is only rarely a sole manifestation of a hereditary neuromuscular junction (NMJ) disorder or congenital myasthenic syndrome, and is therefore unlikely. One such recently described congenital myasthenic syndrome/dHMN overlap is due to mutations in synaptotagmin 2 (*SyT2*), manifesting with distally dominant weakness, foot deformities, and presynaptic NMJ dysfunction on post-exercise compound muscle action potential (CMAP) amplitude testing.[4] Foot drop can be the dominant manifestation of hereditary distal myopathies such as myofibrillar myopathy and *GNE* myopathy.[5] Myofibrillar myopathies are clinically and genetically (genes associated include *MYOT*, *DES*, *CRYAB*, *ZASP*, *FLNC*, and *BAG3*) heterogeneous disorders characterized by progressive muscle weakness with typical onset in mid-adulthood.[5] *GNE* myopathy typically presents with weakness of ankle dorsiflexion in early to mid-adulthood.[6] Differentiating a distal myopathy and dHMN can be challenging. Frequently, initially affected upper extremity muscles include intrinsic hand muscles in dHMN and forearm/finger flexors in distal myopathies.[2] However, as in the current case, when the patient presents with isolated foot drop, diagnosis based on phenotype becomes difficult and warrants further evaluation such as electrodiagnostic testing, which can be key for etiologic delineation.

Investigations in our patient revealed a normal serum creatine kinase (CK) level, hemoglobin A1c level, thyroid function, vitamin B_{12}, and protein immunofixation electrophoresis. Nerve conduction studies showed a low amplitude tibial CMAP, with otherwise normal motor and sensory conduction studies for age. EMG examination revealed increased abnormal spontaneous activity and severely reduced recruitment of tibialis anterior and medial gastrocnemius muscles (table). These findings were suggestive of chronic axonal neuropathy.

Question for consideration:

1. What further investigations should be considered?

GO TO SECTION 3

Section 3

Based on the clinical presentation, family history, and electrodiagnostic results, dHMN was strongly considered in our patient. He underwent next-generation sequencing and deletion/duplication analysis targeted to genes known to be associated with hereditary neuropathies, which showed a heterozygous variant of unknown significance (p.Pro682-Leu; c.2045C>T) in *MED25* (mediator complex subunit 25). The *MED25* gene is associated with CMT disease type 2B (CMT2B). CMT2B is an autosomal recessive axonal neuropathy characterized by distal weakness, mild sensory loss, and normal or near normal nerve conduction velocities. Disease manifestation occurs only in a homozygous or compound heterozygous state, making this an unlikely explanation in our patient.[7] We proceeded with whole-exome sequencing (WES) for precise diagnosis. WES revealed a heterozygous known pathogenic variant p. Ser60Cys (c.179C>G) in the *MYOT* gene. This has been reported previously in patients with myofibrillar myopathy. This variant is not observed in large population cohorts and functional studies indicate that S60C results in the reduced degradation of myotilin.[8]

Discussion

The *MYOT* gene located on chromosome 5q31 encodes myotilin and causes myotilinopathy, which accounts for about 10% of cases of myofibrillar myopathies.[9] Myotilin is a sarcomere Z-disk component that interacts with α-actinin, filamin C, and actin and plays a role in myofibrillar assembly. It is expressed strongly in skeletal and weakly in cardiac muscles. Mutations in *MYOT* were first identified in autosomal dominant limb-girdle muscular dystrophy type 1A and subsequently in distal myopathies (myotilinopathy). Distal lower extremity weakness is a common presentation of myotilinopathy, seen in about 80% of patients, with an age at presentation between 45 and 60 years. Other features include myalgia, muscle cramps, tight heel cords, hyporeflexia, and normal or slightly elevated CK levels.[5,10] Involvement of the soleus muscle followed by the tibialis anterior and medial gastrocnemius is commonly noted on muscle MRI. EMG shows abnormal spontaneous activity, such as fibrillation potentials, positive sharp waves, complex repetitive discharges, or myotonic discharges. Concomitant peripheral nerve involvement may occur as myotilin is also expressed in peripheral nerve.[10]

Our patient's clinical and electrophysiologic features were suggestive of dHMN. Genetic testing that is focused on a small set of genes known to be associated with the phenotype of interest is rationale and advocated. Nonetheless there can be significant phenotypic overlap between diagnostic categories. In such instances, a broader genetic testing approach can be helpful. WES uncovered the diagnosis of myotilinopathy in our patient with a phenotype mimicking dHMN. In retrospect, EMG findings in our patient could have been consistent with myotilinopathy rather than dHMN. Advanced myopathies may be accompanied by decreased motor unit recruitment, while clear evidence of reinnervated motor units (characteristic of chronic motor neuropathies) was lacking in this patient. Mixed myopathic and neurogenic patterns of motor unit morphology have also been reported with myotilinopathy.[10] Our patient had no history or symptoms or signs of cardiac dysfunction. However, as asymptomatic cardiomyopathy has been described with myotilinopathy,[10] screening echocardiography was included in care recommendations. Muscle biopsy could provide additional insights pertaining to distinction between a dHMN, distal myopathy, or a combination thereof. However, muscle biopsy was not pursued in our patient as it would not have affected the diagnosis of myotilinopathy or management.

Distal myopathies such as myotilinopathy should be considered when evaluating a patient with isolated foot drop. A proportion of cases of suspected dHMN may actually be distal myopathies, and broader genetic testing targeting distal myopathies as well as dHMN can be considered when evaluating such patients.

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Appendix Authors

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Stephan L. Zuchner. MD	University of Miami, FL	Author	Revising the manuscript, study concept
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