

Clinical Reasoning: A 34-year-old woman with recurrent bouts of acral paresthesias

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SECTION 1

A 34-year-old, previously healthy woman presented with a 3-year history of persistent numbness and tingling in her feet ascending to the knees. She was a lifelong long-distance runner, and she normally experiences numbness and tingling in both feet while running that resolve within minutes of stopping her exercise.

Three years ago, she developed diarrhea that was followed a week later by paresthesias in her feet and legs with a stocking distribution to the knees. Her symptoms were associated with a transient feeling of overwhelming fatigue, limiting her ambulation to 1 city block. She did not, however, have any functional weakness. After 2 weeks, milder hand and left face paresthesias developed. Four weeks later, her symptoms plateaued and persisted. Three months later, she developed more intense paresthesias and a sensation of “crawling” below both knees. At that time, she was seen at another hospital, where the examination showed bilateral pes cavus and hammertoes. There was no nerve thickening. Cranial nerves were

intact. Strength was normal except for mild bilateral thenar weakness and slight difficulty with heel walking. The deep tendon reflexes were decreased at the arms and ankles. There was decreased pinprick sensation in the feet in a stocking-glove distribution with hyperalgesia. Vibration was moderately diminished at the ankles.

Nerve conduction studies and electromyography (NCS/EMG) at that time showed uniform, mild conduction velocity slowing of both sensory and motor conduction with borderline prolonged distal latencies in the median and ulnar nerves. She was treated with a 1-month taper of prednisone beginning with 80 mg daily. The crawling sensation resolved and the paresthesias became less intense and stabilized. She was able to resume distance running, but still had persistent, mild numbness in her feet with bouts of increasing intensity every several months. Three years later, the patient presented to us for a second opinion.

Question for consideration:

1. What is the differential diagnosis?

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SECTION 2

The acute onset of acral paresthesias after an episode of diarrhea raises the possibility of Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy). The patient did not seek medical attention at that time. If she had, CSF examination would have been helpful in making the diagnosis. For example, a marked elevation in CSF protein, although nonspecific, is suggestive of an acquired demyelinating polyneuropathy. Her symptoms resolved but recurred 3 months later. This recurrence of symptoms makes Guillain-Barré syndrome less likely. Several clinical and electrophysiologic clues can help the clinician differentiate acquired from inherited neuropathies. Clinically, patients with inherited neuropathies present with a long, slowly progressive history, while patients with acquired neuropathies usually present with more acute or subacute weakness and sensory changes. Foot deformities such as pes cavus and hammertoes are usually indicative of an inherited neuropathy. Paresthesias and tingling are generally seen in acquired polyneuropathies, while painless loss of motor and sensory function are usually observed in hereditary motor and sensory neuropathies. Motor nerve conduction studies in inherited neuropathies are usually uniformly slow, with no temporal dispersion or conduction block. Acquired polyneuropathies frequently have focal slowing or conduction block in a multifocal and segmental pattern on the nerve conduction studies. It should be kept in mind that rare cases of Charcot-Marie-Tooth 1C (CMT1C), as well as hereditary neuropathy with liability to pressure palsies (HNPP) and X-linked Charcot-Marie-Tooth (CMTX), may have multifo-

cal conduction block or temporal dispersion mimicking chronic inflammatory demyelinating polyneuropathy (CIDP).

In our patient, the conduction velocity slowing of both sensory and motor conduction with preserved motor response amplitude is suggestive of demyelinating polyneuropathy. The clinical course suggested an acquired, distal, symmetric sensory variant of CIDP. In addition, the response to steroids reported by the patient raises the possibility of an immune-mediated demyelinating neuropathy. Other forms of immune-mediated demyelinating polyneuropathy that could be included in the differential diagnosis include polyneuropathy with antibodies to myelin-associated glycoprotein (anti-MAG), which is uncommon before the sixth decade; CIDP with or without IgA or IgG monoclonal gammopathy of unknown significance (MGUS); and multifocal motor neuropathy (MMN), characterized by multifocal motor involvement. In the presence of systemic involvement, one should consider POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy or edema, M protein, and skin changes). The patient presented here did not have features suggestive of POEMS.

On the other hand, the presence of pes cavus and hammertoes suggests a chronic peripheral neuropathy despite the relatively short duration of symptoms. Furthermore, the uniform slowing on nerve conduction studies suggest a demyelinating form of Charcot-Marie-Tooth (CMT) disease.

Question for consideration:

1. What further evaluation should be obtained?

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SECTION 3

At this point, a detailed familial history should be obtained, keeping in mind that sporadic genetic mutations are possible. In 2008, the American Academy of Neurology issued an evidence-based practice parameter on the laboratory and genetic evaluation of distal symmetric polyneuropathies.¹ Based on this practice parameter, patients with a distal symmetric polyneuropathy may undergo screening laboratory tests. The tests that provide the highest yield are blood glucose, serum B12 with methylmalonic acid, and serum protein immunofixation electrophoresis. Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype. Genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities, such as CMT1A duplication/HNPP deletion (severe demyelinating), Cx32 (GJB1) (mixed axonal and demyelinating), and MFN2 (axonal) mutation screening.

When the patient presented to us 3 years after the initial onset of symptoms, she reported persistent, mild numbness in her feet with bouts of increasing intensity every several months. She never stopped her long-distance running. A detailed personal and familial history showed that she had normal developmental milestones, particularly no delay in walking. Apart from her brother, who also had foot numbness, the family history was negative. She had 2 children with no neurologic complaints. Repeat EMG/NCS showed mild, uniform slowing of sensory and

motor conduction, prolonged peroneal F wave minimal latencies, no conduction block, and normal needle EMG of the leg (table). In order to rule out other causes of demyelinating polyneuropathies, laboratory tests were performed, including routine chemistries and blood count; hemoglobin A1C (diabetes may be associated with a demyelinating neuropathy); anti-MAG (NCV show diffuse slowing but distal latencies are usually markedly increased); antibody GM1 (which can be increased in patients with acquired, demyelinating polyneuropathies, and particularly motor neuropathies); quantitative immunoglobulins; immunofixation (IgM MGUS is usually associated with demyelinating polyneuropathy with MAG or Waldenstrom macroglobulinemia); B12 and Lyme ELISA (usually associated with axonal neuropathy but demyelinating neuropathies may occur); cryoglobulin (cryoglobulin-associated neuropathies may have motor conduction slowing); and erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF). All of these were negative or normal.

Because of the negative evaluation for acquired causes of neuropathies, the presence of hammertoes and pes cavus, and the uniform slowing of sensory and motor conduction, the diagnosis of CMT neuropathy was entertained and genetic testing was performed. Patients with intermediate motor nerve conduction studies could have mutations in DNMT2 (dynamitin2) and YARS (tyrosyl-tRNA synthetase), PMP22, MPZ, MFN2 (mitofusin 2), NEFL (neurofilament light), GJB1/Cx32 (gap junction protein, beta-1 gene), or GDAP1 (ganglioside-induced differentiation-associated protein 1 gene).² Testing for each of these genes is neither practical nor cost-effective. If an inheritance pattern could be identified, one could test for specific genes accordingly. In our patient, however, the family history was unclear (no symptoms in her family apart from her brother). Relying on clinical and electrophysiologic data are helpful but can be misleading. Mutation in the same gene can result in different phenotypes, even within the same family. To determine which genetic tests to perform, the physician is guided by a combination of clinical and electrophysiologic findings, and on the relative frequencies of known gene defects. Thus, testing for PMP22, MPZ, and Cx32 mutations will lead to a diagnosis in 66% of the patients with inherited neuropathies,³ and is reasonable when motor conduction slowing is evident on NCS.

In our patient, MPZ variant 1 showed an 8–base pair deletion at the nucleotide position 130–137 and the codon position 44–46, which resulted in a frameshift mutation. Cx32 (GJB1) and PMP22 analysis showed no sequence alteration. Genetic testing

Table Nerve conduction studies showing mild, uniform slowing of sensory and motor conduction

Nerve stimulation	Recording site	Latency, ms	Amplitude, μ V	Velocity, ms
Sensory NCS				
R median (digit II)	Wrist	3.6	22	49
R ulnar (D5)	Wrist	3.7 ^a	10	41 ^a
R sural (calf)	Lat mall	4	25	39
R superior peroneal	Ankle	4.7 ^a	9	34 ^a
Motor NCS				
R median wrist	APB	3.7	12.6	
Elbow	APB	8.9	12.2	42.3 ^a
R ulnar wrist	ADM	2.9	10.4	
Below the elbow	ADM	7.8	9.1	47.4
Above the elbow	ADM	10.4	8.3	46.2 ^a
R comm peroneal ankle	EDB	4.3	4.6	
R comm peroneal B fib head	EDB	15.7	2.9	30.7 ^a
R comm peroneal A fib head	EDB	18.4	2.8	29.6 ^a

Abbreviations: ADM = abductor digiti minimi; APB = abductor pollicis brevis; comm = common; EDB = extensor digitorum brevis; fib = fibular; NCS = nerve conduction studies.

^aAbnormal values.

for mutations in the above genes was negative in the patient's mother.

DISCUSSION Our patient's initial presentation of acute acral paresthesias after an episode of diarrhea raised the possibility of acute inflammatory demyelinating polyneuropathy. Later, the initial response to prednisone was consistent with an inflammatory polyneuropathy. In addition, there was no clear familial history apart from the brother who had foot numbness.

However, symptoms of numbness in her feet while running for several years and the presence of hammer-toes and pes cavus on examination suggested CMT. This was further supported by generalized and uniform slowing on nerve conduction studies and the negative evaluation for acquired causes of neuropathies. CMT is classified as demyelinating (CMT1) when the median or ulnar nerve motor conduction velocities are less than 25 m/s and axonal (CMT2) when the median NCV are above 42 m/s. Application of the term "intermediate" to describe NCVs in the 25–42 m/s range can be confusing since NCVs in affected individuals with CMT types 1 or 2 can also lie in that range, and because of the overlap of values in axonal CMT2A and the demyelinating form of CMT and CMT1A.² The term "intermediate" is correctly applied to the form of CMT and not the NCV value. Intermediate forms of CMT should also have evidence of both demyelinating and axonal pathology.²

Peripheral myelin protein zero (MPZ) accounts for more than half of the peripheral nervous system myelin. It plays an essential role in myelination, particularly in myelin compaction, which is related to its homophilic adhesion properties.⁴ Mutations in the MPZ gene, located on 1q22, account for about 5% of patients with CMT.⁵ Transmission is usually autosomal dominant, but sporadic cases occur.⁶

Our patient had an 8-bp deletion at the nucleotide position 130–137, resulting in a frameshift mutation of MPZ. This mutation predicts an autosomal dominant form of CMT. In this family, it appeared as a novel mutation, which is common for MPZ.⁷ To our knowledge, this frameshift mutation has not been described.

More than 95 different mutations (mostly point mutations) in the MPZ gene have been identified so far. Thirteen are caused by a frameshift mutation.⁸ Mutations in the MPZ gene are associated with a great variety of clinical phenotypes, ranging from a severe disease with onset of weakness and sensory loss (e.g., Dejerine-Sottas syndrome) to a mild form of demyelinating neuropathy with or without papillary involvement (CMT1B) or an axonal neuropathy (CMT2).

Genetic testing is required to confirm the diagnosis and identify the specific subtype. The site of the mutation is thought to predict the severity of the disease. An evaluation of 73 patients with CMT1B related to mutations in the MPZ showed that most patients presented with either an early onset or a late onset neuropathy.⁶ The type of frameshift mutation that was observed in our patient appears to cause a mild form of CMT. The acute exacerbations (i.e., the paresthesias) may be precipitated by a viral infection. It is unclear if the resolution of these sensory symptoms is part of the natural history of the disease or is secondary to the steroids. The response to prednisone has been described previously in patients with CMT1, where sudden deterioration in symptoms was relieved by steroids or IVIg.⁹ This could be explained by the lymphocytic infiltration of the nerve that occurs in some cases of CMT.¹⁰

DISCLOSURE

Dr. Karam serves on the editorial team for the *Neurology*[®] Resident & Fellow Section. Dr. Scelsa reports no disclosures.

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