Clinical Reasoning:
A patient with rapidly progressive sensory loss and imbalance

SECTION 1
A 52-year-old man presented with sudden onset of acral paresthesia and imbalance. The patient did not have any recent illness, sick contacts, or travel abroad. He denied weakness, pain, bowel or bladder incontinence, dysphagia, dysarthria, or shortness of breath. On neurologic examination, 1 month into his symptoms, he had reduced muscle strength in his finger spread, extension, and flexion on both sides graded on Medical Research Council scale 4/5 and in toe extensors −4/−4 and toe flexors −4/4. The rest of his muscle strength was normal. Reflexes were absent throughout. He had reduced sensation to all modalities in a length-dependent pattern up to his midshin and wrists on both sides. He was severely unsteady when walking and he could not tandem. Romberg was positive. The rest of his neurologic examination was normal apart from high arches and hammertoes. The patient had a family history of Charcot-Marie-Tooth disease type 1A (CMT1A) (PMP22 duplication) and was himself tested, although asymptomatic, and was also found to be carrying the mutation.

Questions for consideration:
1. What is your preliminary differential diagnosis?
2. What initial investigations would you propose for this patient?
SECTION 2

Despite the genetically confirmed \textit{PMP22} mutation, the rapid onset and progression of this patient’s symptoms are concerning. A superimposed process should be considered and ruled out. For example, the patient can have a superimposed inflammatory polyneuropathy such as Guillain-Barre syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or a paraneoplastic or neoplastic neuropathy. Certain toxic exposures such as arsenic poisoning can cause subacute neuropathy with a similar presentation. Infectious agents such as Lyme disease, HIV, and hepatitis C can cause subacute GBS-like presentations. Vasculitis can cause sensory disturbance, although it typically presents with painful multifocal neuropathy. Meningeal carcinomatosis can present with rapid motor and sensory disturbance including cranial neuropathies. Finally, a central process such as a cervical cord lesion caused by spinal stenosis or a demyelinating lesion can cause similar bilateral sensory disturbance, although the absence of upper motor neuron signs and a sensory level do not support this.

To narrow the diagnosis, the patient underwent additional testing, including nerve conduction study and EMG, MRI of the spine, and CSF examination. Nerve conduction studies showed absent sensory responses of the upper and lower limbs with demyelinating features of the motor responses (figure 1, table 1).

Table 1 demonstrates markedly prolonged motor distal latencies (DL) (DL in the arms 16–27 ms [normal < 4.2 ms], DL in the legs 14–26 ms [normal < 5.7 ms]). Marked prolonged compound muscle action potential durations as seen in the left median (45 ms at distal site and 50 ms at proximal site) and tibial nerves (47 ms at distal site and 53 ms at proximal site) are consistent with temporal dispersion. On needle EMG, there was abnormal spontaneous activity in the form of fibrillation potentials in the distal legs and long-duration, high-amplitude, polyphasic motor unit potentials with reduced recruitment in all muscles tested. A lumbar puncture was performed to rule out an infectious etiology and meningeal carcinomatosis. CSF protein was 70 mg/dL, CSF glucose was normal, cell count was 0. A complete spine MRI revealed mild enhancement of the cervical and lumbar roots.

Additional blood tests were performed to rule out other acquired causes of neuropathy. CSF immunoglobulin G index, oligoclonal bands, CSF Venereal Disease Research Laboratory (VDRL),

\begin{table}[h]
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\begin{tabular}{|l|l|l|l|l|l|}
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Nerve stimulation & Recording site & Latency, ms & Amplitude, $\mu$V & Velocity, ms & Duration, ms \\
\hline
L median & Wrist & $27.0 < 4.4$ & $1.5 > 4.2$ & $18.0 > 49$ & $45.0$ \\
L median & Elbow & $39.7 > 4.0$ & $1.0 > 4.2$ & & \\
L median F response, ms & Wrist & Absent & & & \\
L tibial & Ankle & $14.4 < 5.7$ & $0.9 > 2.8$ & $11.0 > 41$ & $47.0$ \\
L tibial & Knee & $49.4 > 6.0$ & $0.3 > 2.8$ & & $53.0$ \\
L tibial F response, ms & Ankle & Absent & & & \\
\hline
\end{tabular}
\caption{Values generated from the motor nerve conduction studies of the left median and tibial nerves}
\end{table}
angiotensin-converting enzyme, vascular endothelial growth factor, GM1 antibody, cryoglobulin, myelin-associated glycoprotein Western blot, hemoglobin A1c, methylmalonic acid, serum immunofixation, serum free light chains, thyroid-stimulating hormone, free T4, complete blood count, B12, sedimentation rate, antinuclear antibodies, extractable nuclear antigen, tissue transglutaminase immunoglobulin A, hepatitis C antibody, Lyme serology, HIV, and hepatitis B surface antigen were all normal or negative.

Question for consideration:
1. What is your diagnosis based on the history, clinical examination, and EMG and laboratory studies?
The uniformly severely slowed conduction velocities are usually consistent with a severe, inherited, demyelinating, sensorimotor peripheral neuropathy such as can be seen in CMT1A. However, the marked temporal dispersion and the reduced recruitment in both distal and proximal muscles are atypical for a patient with asymptomatic CMT1A. Temporal dispersion can sometimes be seen in inherited neuropathies, but the degree of temporal dispersion seen in this patient suggests the presence of a superimposed inflammatory process.

The acute onset of paresthesia and imbalance along with the nerve conduction and EMG findings are highly suggestive of a superimposed acquired inflammatory and demyelinating process. The workup ruled out any infectious, paraneoplastic, neoplastic, or metabolic causes. The mildly elevated CSF protein with albuminocytologic dissociation can be seen in either acquired or inherited processes. The patient presented with 4 weeks of progressive symptoms. He did not meet the time course for the diagnosis of CIDP, which is defined as a progression of symptoms for more than 8 weeks. This patient met all the mandatory electrophysiologic criteria\(^1\) for acute inflammatory demyelinating polyneuropathy/CIDP, which require only 3 of 4 of the following:

1. Significant reduction in motor nerve conduction velocity in 2 or more motor nerves:
   a. \(<80\%\) of lower limit of normal (LLN) if CMAP \(>80\%\) of LLN
   b. \(<70\%\) of LLN if CMAP \(<80\%\) of LLN
2. Partial conduction block or abnormal temporal dispersion in one or more motor nerves: peroneal nerve between ankle and below fibular head, median nerve between wrist and elbow, or ulnar nerve between wrist and below elbow
   a. Criteria suggestive of partial conduction block: \(<15\%\) change in duration between proximal and distal sites and \(>20\%\) drop in negative peak (\(-p\)) area or peak-to-peak (p-p) amplitude between proximal and distal sites
   b. Criteria for abnormal temporal dispersion and possible conduction block: \(>15\%\) change in duration between proximal and distal sites and \(>20\%\) drop in \(-p\) area or p-p amplitude between proximal and distal sites
3. Significant prolongation of distal motor latency in 2 or more motor nerves:
   a. \(>125\%\) of upper limit of normal (ULN) if CMAP \(>80\%\) of LLN
   b. \(>150\%\) of ULN if CMAP \(<80\%\) of LLN
4. Significant prolongation or absence of F-waves in 2 or more motor nerves:
   a. \(>120\%\) of ULN if CMAP \(>80\%\) of LLN
   b. \(>150\%\) of ULN if CMAP \(<80\%\) of LLN

The patient also fulfilled mandatory CSF study findings as he had cytoalbumin dissociation and negative CSF VDRL.

Questions for consideration:

1. What treatment would you propose in this situation?
2. What findings would you expect on repeat EMG studies after treatment?
SECTION 4

The most widely used treatments for inflammatory neuropathy such as CIDP consist of IV immunoglobulin (IVIg), plasma exchange, and corticosteroids.2 The treatments appear to be equally effective in studies performed over time. The initial dose of IVIg is typically 2 g/kg infused over 4 to 5 days, as was the case with this patient. Pulse IV methylprednisolone (1,000 mg/day) for 3 days can be given with tapering doses given once weekly, then once monthly. The therapy is initiated early in the course of the disease to prevent continuing demyelination and secondary axonal loss leading to permanent disability.2 Our patient was treated with IVIg with complete resolution of his symptoms and normalization of his examination, including deep tendon reflexes.

The benefit of treatment is seen in improvement of mobility and strength as well as the return of sensory disturbance to baseline. With treatment of demyelinating peripheral neuropathies, the examiner can see in follow-up studies direct recovery of distal latency, duration, amplitude, and conduction velocity, as noted in figure 2. In consideration of the long-term, sustained improvements in axonal excitability and other measures, clinical improvement seen with long-term IVIg therapy may reflect improvements in biophysical properties and possibly even promotion of remyelination and prevention of secondary axonal degeneration (table 2).3

DISCUSSION

The challenge of this case highlights 2 separate pathologic processes that typically do not occur together. The typical findings of a hereditary neuropathy include symmetric distal limb weakness and negative sensory symptoms, isolated absent Achilles or diffusely reduced or absent reflexes, pes cavus, hammertoes, symmetrically and uniformly slowed nerve conduction velocities, and a family history of neuropathy. The stereotypical findings of an acquired neuropathy include symmetric or asymmetric distal or proximal weakness and positive sensory symptoms, diffusely absent reflexes, asymmetric and nonuniformly slowed nerve conduction velocities, and temporal dispersion or conduction block at noncompressive sites. The patient presented herein had both hereditary and acquired neuropathies. An observation such as this case has been described previously, with the authors postulating that patients may have an inflammatory-demyelinating hereditary motor and sensory neuropathy.4

Table 2

<table>
<thead>
<tr>
<th>Nerve stimulation</th>
<th>Recording site</th>
<th>Latency, ms</th>
<th>Amplitude, μV</th>
<th>Velocity, ms</th>
<th>Duration, ms</th>
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<tr>
<td>L median</td>
<td>Wrist</td>
<td>8.8 &lt; 4.4</td>
<td>6.3 &gt; 4.2</td>
<td>27 &gt; 49</td>
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<td>L median</td>
<td>Elbow</td>
<td>17.1 &gt; 4.0</td>
<td>5.6 &gt; 4.2</td>
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<tr>
<td>L median F response, ms</td>
<td>Wrist</td>
<td>44 &lt; 31</td>
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<td>L tibial</td>
<td>Ankle</td>
<td>7.3 &lt; 5.7</td>
<td>4.2 &gt; 2.8</td>
<td>21 &gt; 41</td>
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<tr>
<td>L tibial</td>
<td>Knee</td>
<td>26.3 &gt; 6.0</td>
<td>2.2 &gt; 2.8</td>
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<td>17</td>
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<tr>
<td>L tibial F response, ms</td>
<td>Ankle</td>
<td>89 &lt; 56</td>
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A question has been proposed over the last decade as to whether patients with hereditary neuropathy are more susceptible to inflammatory neuropathy than the general population. It has been suggested and accumulating evidence exists4–9 for a superimposed inflammatory process in a subgroup of patients with CMT disease that is not genotype-specific. It could be related to genetic susceptibility or may relate to a disturbance of the normal function of the protein encoded by the affected gene. The take-home message is that if a patient with CMT disease experiences an acute or subacute deterioration in clinical condition, a search for other causes should be undertaken, and treatment of a coexistent inflammatory neuropathy with immunotherapy should be considered.10

AUTHOR CONTRIBUTIONS

Eric Lee: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Chafic Karam: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Nizar Chahin: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision.

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REFERENCES

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