

## CLINICAL CARE CONUNDRUMS

## Unnerving

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.



This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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A 73-year-old African American man presented to his primary care physician's office concerned about several years of muscle cramps throughout his body as if his "nerves were jumping" and 1 month of bilateral arm weakness.



For the past 10 years, he had experienced intermittent cramping in his calves and thighs, described as a slow tightening of the muscles associated with mild pain. Initially, the cramps lasted less than 5 minutes, occurred every few days at various times of the day, and might awaken him from sleep. They happened more often following periods of inactivity and on occasion would resolve after playing golf. In recent weeks, the sensations became more frequent, more diffuse, and lasted up to several hours. He described them as a "shivering." They began to affect his biceps, pectorals, deltoids, forearms, back, and calves, and would occur unrelated to activity or inactivity. He denied sensory disturbances, facial twitching or facial weakness, diplopia, dysarthria, dysphagia, dyspnea, changes in bowel or bladder function, unexplained lapses of consciousness, fevers, or weight loss.

Long-standing cramping is nonspecific and may reflect transient electrolyte derangements or muscle overuse. However, the more recent change in frequency, duration, and quality of these sensations, along with the reported weakness, raises concern for a process involving the peripheral nervous system. It will be important to differentiate cramping from other abnormal movements such as fasciculations, tremor, or myoclonus, and to determine whether there is objective weakness on the neurological examination.



His past medical history was significant for coronary artery disease with an ST-segment elevation myocardial infarction several years prior, which was treated with a drug-eluting stent. He was also diagnosed with essential thrombocythemia at the time of his myocardial infarction and tested positive for the JAK2 mutation. He was treated for several years with hydroxyurea following his diagnosis

of essential thrombocythemia. Hydroxyurea had been discontinued 6 months prior due to cytopenias. The remainder of his history was significant for hypertension, chronic kidney disease stage 3, and prediabetes.



Medications were clopidogrel, atorvastatin, metoprolol, lisinopril, and hydrochlorothiazide. He did not use tobacco nor consume alcohol or illicit drugs, and he drank caffeine only occasionally. He had no family history of neurologic disorders.

Apart from his use of statins, which often affect muscles (and less commonly the nerves), the past medical history provides minimal additional insights into the cause of his symptoms. If weakness is detected on physical exam, the next step would be to distinguish upper (central) from a lower motor neuron (peripheral) localization. A diffuse problem involving all 4 limbs is generally more likely to arise from a disorder of a lower motor neuron (LMN) structure (anterior horn cell, nerve, neuromuscular junction, or muscle). To explain bilateral symptoms of the upper and lower limbs, an upper motor neuron (UMN) disease would have to affect the bilateral brain or cervical cord, a somewhat less likely possibility given the cramps described. It would also be quite unusual to have weakness of central nervous system origin without sensory deficits.



On physical examination, the patient was well-appearing and in no apparent distress. Temperature was 98.1, blood pressure 134/84, pulse 110 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation was 100% while breathing ambient air. There was no lymphadenopathy. Lung, heart, abdominal, and skin exams were unremarkable. He was alert and oriented. His speech was without dysarthria. Examinations of the cranial nerves were intact. No tongue atrophy or fasciculations were noted. No pooling of secretions was appreciated in the oropharynx. Examination of the musculature revealed normal tone, strength, and bulk. However, there were diffuse fasciculations present, most prominent in the bilateral biceps, pectorals, deltoids, forearms, upper back, and calves. Sensation to light touch, temperature, and vibration were intact. Babinski's sign was absent, and deep tendon reflexes were normal, except at the ankles where they were reduced. Coordination and gait were normal.

The exam is notable for diffuse fasciculations, defined as spontaneous local involuntary muscle contraction and relaxation, which is often visible. Benign fasciculations are extremely common, with up to 70% of otherwise healthy

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adults experiencing them, and may be brought on by physical exertion. Men experience these benign fasciculations more frequently than women, and they can occur at any age and persist throughout life. Fasciculations may point to LMN disease, usually localizing to the anterior horn cell (for instance in amyotrophic lateral sclerosis [ALS]), muscle, or nerve disorders (including diffuse polyneuropathy). The presence of fasciculations in patients without other complaints and an otherwise normal physical examination supports benign fasciculations. The presence of neurologic deficits, however, such as weakness or reflex loss, is worrisome for another etiology. The absence of sensory changes makes anterior horn cell disease or myopathy most likely, as pure motor neuropathies are uncommon.

The fasciculations in this patient are most prominent in the proximal muscles, which may indicate a primary muscle disorder. Myopathies are typically characterized by diffuse symmetric weakness that is more proximal than distal, with no changes in sensation or deep tendon reflexes. One muscle disease characterized by fasciculations and cramping is periodic paralysis, which is often associated with potassium abnormalities or thyroid dysfunction caused by specific channelopathies. However, patients with this disorder typically present with episodic crises in contrast to the constant symptoms in this case.

Given the accelerated tempo of this patient's symptoms, further diagnostic evaluation should include basic laboratory testing including electrolytes, creatinine kinase, and thyrotropin. If these initial tests fail to reveal an etiology, the next study of choice would be an electromyography (EMG) and nerve conduction study (NCS), which can definitively localize the disorder to and within the peripheral nervous system. Unlike in UMN disease, in which neuroimaging is crucial, imaging is unlikely to be informative in patients with an LMN disorder.

 Results of a complete blood count demonstrated a platelet count of 590,000/ $\mu$ L (normal 140–400 K/ $\mu$ L), but was otherwise normal. Sodium, potassium, magnesium, and calcium levels were normal as were alanine aminotransferase, thyrotropin, and urinalysis. The hemoglobin A1c was 6.4%. Serum creatinine kinase was 157 U/L (normal <170 U/L), and the serum creatinine was 1.7 mg/dL, similar to previous results. The erythrocyte sedimentation rate was 58 mm/h (normal 0–20 mm/h). Magnetic resonance imaging (MRI) (Figure 1) of the cervical spine demonstrated diffuse disc desiccation, and multilevel spondylosis most prominent at C4–C5 and C5–C6, with severe central canal stenosis and neural foraminal narrowing.

The routine laboratory tests do not point to an obvious cause of this man's symptoms. As expected, the MRI findings do not explain diffuse fasciculations in all limbs with no sensory disturbance. Further evaluation should include EMG and NCS.

 NCS of the median and ulnar nerves demonstrated minimally reduced conduction velocities and markedly prolonged latencies. Sensory responses were absent. No conduction block was detected. EMG demonstrated fasciculations of the right extensor digitorum and first dorsal interossei, as well as decreased amplitude and decreased recruitment of motor units.




**FIG. 1.** Magnetic resonance imaging of the cervical spine demonstrating diffuse disc desiccation, and multilevel spondylosis most prominent at C4–C5 and C5–C6 with severe central canal stenosis and neural foraminal narrowing.


Abnormalities on the EMG testing can reflect either a primary muscle disorder or muscle derangement resulting from disease of the nerves. NCSs are important to differentiate these 2 possibilities. This patient's NCS indicates that the primary process is a diffuse motor and sensory neuropathy, not myopathy. The lack of sensory findings on physical examination emphasizes the ability of electrodiagnostic testing to extend the clinical neurologic examination in some cases. Markedly prolonged latencies and more modest reduction in amplitude support a motor and sensory neuropathy mostly due to demyelination, rather than axonal loss, and that it is more severe in the lower limbs.

Among the demyelinating neuropathies, acute inflammatory demyelinating neuropathy (Guillain-Barré syndrome), is the most commonly recognized. The prolonged time course of this patient's illness excludes this possibility. Chronic inflammatory demyelinating polyneuropathy is also very unlikely in the absence of conduction block on NCS. Demyelinating neuropathies may also result from antibody-mediated nerve injury. The serum paraprotein most commonly involved is immunoglobulin M (IgM), as is detected in neuropathy due to antibodies to myelin-associated glycoprotein (anti-MAG) neuropathy. Another variant is the ganglioside monosialic acid antibody (anti-GM1) associated with a rare disease called multifocal motor neuropathy (MMN), an important condition to recognize because symptoms of this illness may mimic the presentation of ALS, often with fasciculations and weakness. Unlike ALS, MMN is very responsive to treatment. Other antibody-mediated neuropathies are much rarer. In this patient, MMN is unlikely because sensory nerves are affected in addition to motor nerves.


Because NCSs also indicate some axonal loss, it would be reasonable to screen for vitamin deficiencies, human immunodeficiency virus, and viral hepatitis. The pattern here is more symmetric and confluent than would be expected if he had mononeuritic multiplex from vasculitis.

 Vitamin E level was normal. Vitamin B12 level was 323 pg/mL (normal >200 pg/mL), methylmalonate 0.3 μmol/L (normal 0–0.3 μmol/L). Antibodies to human immunodeficiency virus and surface antibody and antigen to hepatitis B were not detected. Cryoglobulins, anti-nuclear antibody, and antibodies to myeloperoxidase and proteinase 3 were not detected. Serum antibodies to tissue transglutaminase and *Borrelia burgdorferi* were not detectable. Serum protein electrophoresis demonstrated 2 small spikes in the gamma region. Quantitative serum immunoglobulin levels were normal except for IgM, which was elevated at 1.7 g/dL (normal <0.19 g/dL). Serum free light chains showed a kappa component of 43.7 mg/L (normal 3–19 mg/L), a lambda component of 13.8 mg/L (normal 5–26 mg/L), and a kappa/lambda ratio of 3.17 mg/L (normal 0.26–1.65 mg/L).

The differential for a symmetric demyelinating neuropathy is quite narrow, and tests for vasculitis, celiac disease, and Lyme disease are not necessary. To pursue the cause of the elevated IgM, specific serum testing should be obtained for anti-MAG antibodies. Many cases of anti-MAG neuropathy are associated with an underlying lymphoproliferative disorder. As such, additional imaging to identify occult lymphoma is warranted.


 Anti-GM1 and asialoganglioside were not detectable. The anti-MAG IgM titer was >102,400 (normal <1:1600). Abdominal ultrasound showed normal sized kidneys with normal cortical echogenicity and no splenomegaly. Computed tomography with contrast was not performed due to chronic kidney disease.

Treatment for anti-MAG neuropathy is evolving rapidly as our understanding of the entity improves. Cyclophosphamide, intravenous immune globulin, and plasmapheresis have been the traditional treatments, but in the past decade, favorable experiences with rituximab have led some to try this medication earlier in the course. Prognosis can be favorable in many patients.

 Over the next 2 months he continued to have fasciculations. He developed progressive generalized weakness, an unsteady gait, required a walker for mobility, and began to have trouble with his activities of daily living. His cognition remained intact. There was no pooling of secretions. Serial neurologic examinations demonstrated persistent fasciculations, progressive atrophy, most notably in the intrinsic hand muscles and legs, and progressive weakness of all limbs, worse in the distal muscle groups. Deep tendon reflexes remained preserved, except at the ankles where they were absent. Sensory exam showed stocking diminution to temperature up to his knees and elbows. Romberg sign was present, and he could not walk without support. He was started on rituximab, and after 4 weeks his condition continued to deteriorate.

The response to rituximab may be delayed. Alternatively, his disease may have an underlying cause such as occult lymphoma not yet identified, which would require treatment

to control the neuropathy. Because of the potential association between lymphoma in some patients with anti-MAG neuropathy, and because he is not responding to immunotherapy, whole body imaging with positron emission tomography and bone marrow biopsy should be performed.

 CD19 levels indicated an appropriate B cell response to rituximab, but the anti-MAG titer remained elevated at >102,400. He received additional doses of rituximab, but continued to decline. A bone marrow biopsy was considered, but the patient opted to forgo the procedure. After several months of rituximab, he developed mild dysarthria and dysphagia and was hospitalized for plasma exchange. After 5 sessions of plasma exchange, he showed no improvement and was discharged to a rehabilitation facility. Over the ensuing months, he became restricted to wheel chair or bed and eventually opted for comfort measures. He died after an aspiration pneumonia 15 months after his initial visit to his physician. Permission for an autopsy was not granted.

## COMMENTARY

When encountering patients with involuntary muscle movements, hospitalists must recognize potential serious underlying disorders and implement a cost-effective evaluation strategy. Fasciculations are a common finding that represent involuntary discharges of a motor unit, with a wide array of causes including radiculopathies, neuropathies, metabolic disturbances, and motor neuron diseases.<sup>1,2</sup> Useful clues might point to a probable cause, such as a statin-induced myopathy in patients with concomitant myalgias, or hypokalemia in patients on loop diuretics. Confinement of fasciculations to specific anatomic structures may be useful, as in carpal tunnel syndrome, where fasciculations would only be expected distal to median nerve compression. Features such as sensory loss, muscle atrophy, or abnormal reflexes should alert the clinician to a possible neurologic lesion.

Although fasciculations rarely reflect serious underlying pathology, the presence of neurologic deficits, such as muscle weakness, abnormal reflexes, or sensory loss, should prompt further investigation.<sup>3</sup> Because fasciculations typically point to an abnormality of LMN structures, a reasonable approach is to measure serum electrolytes, creatinine kinase, and thyrotropin to evaluate for myopathy. If these tests are unrevealing, the next step would be to perform EMG and NCS to help localize the lesion among the LMN structures. Muscle localization could then be pursued with muscle biopsy. Alternatively, when electrodiagnostic testing indicates peripheral nerve pathology, further evaluation is guided by the type of neuropathy: demyelinating, axonal, or mixed. If electrodiagnostic and clinical findings are unrevealing, the patient is diagnosed with benign fasciculations.

Demyelinating neuropathy, as seen in our patient, is relevant to hospitalists for several reasons. First, the list of diagnostic possibilities is narrow, allowing hospitalists to forgo many unnecessary laboratory tests and brain MRI. Second, unlike many axonal neuropathies, demyelinating neuropathies are potentially reversible if recognized early and promptly treated. Third, demyelinating neuropathy may involve the diaphragm, necessitating vigilance for neuromuscular respiratory failure. Finally, hospitalists need to be aware that some demyelinating neuropathies are associated with underlying malignancy, and identifying and treating the primary cancer may be critical to ameliorating the neuropathy.<sup>4–8</sup>



IgM paraproteinemia, with or without an underlying malignancy, is 1 type of demyelinating neuropathy that is potentially reversible with early treatment. The typical patient is exemplified by the case presented in this report: an older man who experiences symmetric, gradually worsening sensory disturbances and ataxia over months to years.<sup>9</sup> Motor deficits may progress more rapidly, prompting patients to seek hospital care.<sup>7,10</sup> The hallmark of NCS in anti-MAG disease is a demyelinating pattern with a predominance of distal abnormalities including marked prolongation of distal motor latencies and reductions in conduction velocities and sensory action potentials.<sup>9</sup> Findings of areflexia or conduction block should prompt consideration of other etiologies, such as acute or chronic inflammatory demyelinating polyneuropathy.

For unclear reasons, IgM is more likely than other immunoglobulins to cause neuropathy. Although IgM accounts for only 17% of monoclonal gammopathies, IgM is detected in 50% to 70% of patients who have both monoclonal gammopathy and peripheral neuropathy.<sup>11</sup> Approximately half of the patients with IgM-associated neuropathy produce antibodies to MAG.<sup>11,12</sup> Several lines of evidence have firmly established the causative role of anti-MAG antibodies.<sup>13</sup>

Because the majority of patients with anti-MAG neuropathy will have no malignant source of IgM paraprotein identified, it is unclear how extensively to search for occult malignancy. A reasonable approach is to perform a bone marrow biopsy to distinguish underlying IgM monoclonal gammopathy of undetermined significance from Waldenström's macroglobulinemia.<sup>14</sup> Bone marrow analysis may also detect B-cell lymphoma, primary amyloidosis, chronic lymphocytic leukemia, and hairy cell leukemia, which have been described in cases of anti-MAG syndrome.<sup>4-8</sup> There are no reports of anti-MAG neuropathy linked to either essential thrombocythemia nor hydroxyurea use.

The goals of treatment in anti-MAG neuropathy are to deplete monoclonal B cells and to reduce antibody levels. Although it is reported that approximately half of patients will improve with some form of immunotherapy, a Cochrane review of randomized controlled trials of treatments for anti-MAG neuropathy (including plasma exchange, intravenous immunoglobulin [IVIg], rituximab, corticosteroids, and chemotherapy) concluded that evidence is lacking to recommend 1 treatment over another.<sup>15</sup> European guidelines suggest deferring therapy unless progressive or severe neuropathy is present, in which case IVIg, plasma exchange, or rituximab may be tried.<sup>14</sup> In patients with underlying malignancy, treatment of the hematologic disorder may improve the neuropathy.<sup>4,8</sup>

Although fasciculations and peripheral neuropathy typically present in outpatient settings, they can be harbingers of more dire diagnoses that prompt patients to seek hospitalization. A sequential and cost-effective approach can allow the astute hospitalist to pinpoint the diagnosis in what might otherwise be an unnerving case.

## KEY TEACHING POINTS

1. Fasciculations are extremely common and usually benign, but may indicate a more serious neurologic process, especially when accompanied by weakness or other neurologic symptoms.
2. Localizing neurologic deficits to upper motor neuron or lower motor neuron structures guides further evaluation.
3. Central nervous system imaging is not indicated in demyelinating neuropathies.
4. Bone marrow biopsy and cross-sectional imaging to evaluate for malignancy should be considered in patients with anti-MAG neuropathy who fail to improve despite therapy.

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