Clinical Reasoning:

A 34-year-old man with recurrent limb weakness

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SECTION 1

A 34-year-old healthy man presented with 3 weeks of progressive bilateral arm weakness. He first noticed weakness while combing his hair and getting dressed. His symptoms were preceded by transient paresthesia in all 5 fingertips of both hands. Over the next 2 weeks, his weakness progressed slowly and spread to his forearms and hands. He never felt numbness or tingling in the feet. There was no visual disturbance, dysphagia, dysarthria, or bladder or bowel disturbance. There was no prodromal illness or vaccination. He took no medications and did not drink, smoke, or use drugs. Familial history was unremarkable. His general examination, including

supine and erect blood pressure and pulse, was normal. The cranial nerves were intact. Strength was 3/5 in both deltoids and 4/5 in remaining muscles of both upper extremities. Neck flexor, extensor, and bilateral lower extremity muscles demonstrated normal muscle strength. Tendon reflexes were all absent apart from reduced bilateral brachioradialis and left triceps reflexes. Sensory tests with pin, cold, vibration, and proprioception had normal results. The rest of his examination, including gait, was normal.

Question for consideration:

1. What is your differential diagnosis at this stage?

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SECTION 2

This patient presented with progressive bilateral arm weakness. The sensory symptoms were subjective, minimal, and resolved eventually prior to treatment. Although the pattern of weakness suggests a myopathy, the clinical examination is more consistent with a motor neuropathy. The absence of the reflexes, in particular in the legs which were strong, makes the diagnosis of myopathy unlikely. Patients with Lambert-Eaton myasthenic syndrome (LEMS) can have absent reflexes which may reappear after exercise, but frequently have autonomic symptoms with weakness mainly in the legs.

The differential diagnosis of an acute motor neuropathy includes the following¹:

1. Idiopathic inflammatory causes such as Guillain-Barré syndrome (GBS), multifocal motor neuropathy (MMN), acute onset chronic inflammatory demyelinating polyneuropathy (CIDP), or acute onset Lewis Sumner syndrome (LSS)
2. Vasculitic conditions, which also include the nonsystemic vasculitic neuropathies
3. Granulomatous conditions such as sarcoidosis
4. Infections or neuropathies associated with infectious processes such as Lyme disease, HIV,

cytomegalovirus (CMV), West Nile virus, and other polio-like causing neuropathies

5. Paraneoplastic syndromes such as those associated with anti-Hu (sensory symptoms predominates) or with non-Hodgkin lymphoma (NHL)
6. Metabolic such as porphyria or diabetes mellitus (the latter is usually painful)
7. Toxic such as lead, botulism, tick paralysis, or dapsone

Since this patient's symptoms are limited to the arms, MMN or LSS are high on the differential diagnosis. LSS is also referred to as multifocal acquired demyelinating sensory and motor neuropathy. It is a possible diagnosis but the sensory symptoms are usually prominent, and the diagnosis cannot be made before 2 months of clinical symptoms. MMN typically present with asymmetric arm weakness. GBS usually presents as an ascending paralysis. Other etiologies are less likely because of the absence of systemic symptoms, toxin exposure, or prior medical history, but still need to be ruled out as neuropathy can be the first or only manifestation of these conditions.

Question for consideration:

1. What is the next step in the management of this patient's symptoms?

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SECTION 3

To narrow the diagnosis, blood and CSF examination and EMG/nerve conduction study (NCS) are necessary. Complete metabolic panel, complete blood count, HbA1C, urine porphyrins, serum protein electrophoresis/immunofixation electrophoresis, C-reactive protein, erythrocyte sedimentation rate, cryoglobulins, GM-1 antibodies, antinuclear antibodies, and rheumatoid factor were all normal or negative. CSF examination showed no lymphocytes, a protein level of 67 mg/dL (normal <60 mg/dL), and a normal glucose level. CSF cytology and serologies for Lyme, CMV, and West Nile virus were negative. CK level was 759 U/L (normal <170 U/L). Serum HIV and human T-cell lymphotropic virus I/II antibodies were not detected. MRI of the cervical spine was normal. EMG/NCS studies showed normal sensory, motor, and late responses recorded in right upper and lower extremities apart from bilateral absence of H-reflexes. Needle EMG of muscles in the right upper and lower extremities showed frequent fibrillations and positive sharp waves in muscles of the upper extremity, both distal and proximal apart from the abductor pollicis brevis, which was not involved. There was significantly reduced recruitment of normal motor units in the biceps and finger extensors. Recruitment in other muscles was within normal limits. The examination of lower extremity, cervical, and thoracic paraspinal muscles was normal. These results suggest a subacute motor denervation in the upper extremities and favor a primarily axonal neuropathy: normal nerve conduction, evidence of denervation on needle EMG with absence of prolonged, high-amplitude, and polyphasic motor unit action potentials. These findings, however, do not completely rule out a demyelinating neuropathy, especially since the H-reflexes were absent. A conduction block, which is an important diagnostic feature of most acquired demyelinating neuropathies, may be missed on routine NCS, especially if the block is proximal. To remediate to this issue, long latency

reflex tests or late responses are typically used to assess these segments. In this patient, however, the F-waves were within normal limits. Note that F-waves (which, in the arms, assess only C8 and T1 pathways) are not sensitive and are of clinical significance only when abnormal, because, by convention, the single fastest response in a group of F-waves is used to measure the minimum. Thus, a single normal axon may generate a normal response. Furthermore, the areflexia and absent tibial H-reflexes, in the absence of any denervation or significant muscle weakness in the legs, favors a demyelinating process. The CSF examination did not suggest infectious or neoplastic conditions. The mildly elevated protein in the CSF is consistent with GBS or MMN. Slightly to moderately increased serum creatine kinase activity is observed in up to 67% of patients with MMN.² At this stage, presumptive diagnosis of motor neuropathy, without any other identified cause, justified the treatment with IV immunoglobulin (IVIg).

The patient was admitted to the hospital and was started on IVIg. His symptoms improved remarkably and he was discharged. Two months later, the patient was readmitted with worse bilateral arm weakness, graded as right/left: deltoids 2/2, biceps 2/3, wrist extensors 3/4, wrist flexors 5-/4+, finger extensors 4-/4-, finger flexors 4+/4+, intrinsic hand muscles 4/4, and extensor hallucis longus 4+/4+. Cranial, neck, and all other lower extremity muscles were normal. There was no atrophy. He could not come up from a squatting position. There were trace bilateral brachioradialis and triceps reflexes with bilateral biceps and lower extremity areflexia. Sensory examination had normal results. There was no muscular atrophy.

Questions for consideration:

1. How does the clinical course narrow the diagnosis?
2. What is the significance of the severe right biceps weakness in the absence of atrophy?

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SECTION 4

The recurrence of the weakness in this patient makes the diagnosis of GBS unlikely. The marked improvement with IVIg rules out MND. The persistence of symptoms beyond 8 weeks raises the diagnosis of LSS. While the absence of sensory findings makes LSS unlikely, the symmetry of the patient's symptoms argues against MMN. The severe biceps weakness, in the absence of atrophy, suggests motor conduction block. A repeat NCS showed focal motor conduction blocks in the right ulnar (50% drop in amplitude), median (70%), and musculocutaneous (80%) nerves between the axillary and supraclavicular sites. The musculocutaneous motor conduction velocities were reduced. There was no temporal dispersion. Sensory nerve action potentials were normal. Needle examination showed occasional fibrillation potentials with markedly reduced recruitment of large motor unit potentials in the

right upper limb muscles. There were occasional fibrillation potentials and large motor unit potentials in lower limb muscles. Cervical paraspinal muscles had large motor unit potentials without fibrillation potentials, whereas thoracic and lumbar paraspinal muscles were normal. MRI of the brachial plexi showed mild enlargement and increased T2 signal involving the brachial plexus and proximal aspects of the radial, median, and ulnar nerves without abnormal enhancement following contrast injection. There was also increased T2 signal of the shoulder muscles suggestive of denervation changes. A fascicular biopsy of the left ulnar nerve was performed at the site of the conduction block in the axilla, confirmed by an intraoperative EMG, which showed no abnormalities of myelinated fibers except for rare thinly myelinated fibers and mononuclear inflammatory infiltrates in the endoneurium. No definite demyelinating changes were seen on teased fibers examination. We felt that those changes were consistent with the diagnosis of MMN (figure). At this stage the leg weakness worsened. The patient was started on cyclophosphamide 1 g/m² IV monthly for 6 months and 0.8 g/kg IVIg was added to his treatment regimen which brought him into remission and made him IVIg responsive, resulting in complete recovery and a normal neurologic examination. His only medication is 0.8 g/kg IVIg once every 5 weeks and his neurologic examination remains normal 3 years later.

Figure Nerve biopsy

(A) Arrow showing individual mononuclear inflammatory infiltrates in the endoneurium and one small lymphocytic collection. (B) The density and size distribution of myelinated nerve fibers is normal except that there is a very rare fiber with myelin that is too thin for the size of the axons (arrows).

DISCUSSION This patient presented with an atypical form of MMN with conduction block. The relative acute onset of the weakness, the absence of nerve conduction abnormalities on the initial NCS, and the fibrillations on needle EMG suggested an axonal form of GBS. Eventually, the clinical course led to the diagnosis of MMN. The absence of sensory findings clinically and on NCS as well as the absence of demyelination on the nerve biopsy differentiates MMN from Lewis-Sumner syndrome or multifocal CIDP.

MMN typically presents with slowly progressive asymmetric distal motor weakness in the upper extremities.³ It is thought to have an immune origin.² It affects men more than women and patients between 30 and 50 years of age.² Early in the disease course, a single nerve or a single nerve branch territory can be affected. Patients frequently complain of cramps that can occur outside clinically affected areas, fatigue, and twitching. Cranial and respiratory nerves are not usually involved. Patients can have leg weakness at onset but eventually the weakness spreads to the arms.³ The diagnosis of MMN is both clinical and electrophysiologic with evidence of

conduction block on NCS. In advanced cases with substantial and confluent denervation atrophy conduction block may be difficult to demonstrate. Some patients with MMN may be mistakenly diagnosed with a lower motor neuron form of amyotrophic lateral sclerosis. The absence of reflexes in 4 limbs and absence of H-reflexes, as seen in our patient, is atypical of MMN, where reflexes are usually preserved, even in the presence of severe weakness. In addition, the symmetry of our patient's weakness is atypical in MMN but possible. The presence of GM1 antibody supports the diagnosis of MMN but is not sensitive as it can be seen in as little as 25% of patients.³ Treatment of MMN relies on IVIg. Furthermore, in some cases where conduction block is not found or the diagnosis remains in question, IVIg may be used as a diagnostic trial.⁴ In contrast to CIDP, steroids do not have a role in MMN and may worsen the patients' weakness.³ Plasmapheresis is not helpful either. Other immunosuppressive therapies such as cyclophosphamide, cyclosporine, and azathioprine have been tried with variable response but there are no double-blind, randomized, placebo-controlled studies to support the use of these medications.⁴

The prognosis of patients with MMN is relatively good in at least two-thirds of patients with a good response to IVIg.⁵ Unfortunately, some patients do not respond to IVIg, and other immunosuppressive therapy should be tried, although evidence for effectiveness is lacking. Finally, the absence of myelin pathology on the biopsy specimen, which was performed at the site of conduction block, confirms the nondemyelinating nature of this disease. MMN is probably not a demyelinating neuropathy and it is suggested that an autoimmune process affecting so-

dium channels in the node of Ranvier may cause the motor conduction block.^{6,7}

AUTHOR CONTRIBUTIONS

Dr. Karam: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Dyck: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. J. K. Englestad: drafting/revising the manuscript, involved with the figure. Dr. MacGowan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision.

DISCLOSURE

Dr. Karam serves on the editorial board of the *Neurology*® Resident & Fellow Section. Dr. Dyck and J.K. Englestad report no disclosures. Dr. MacGowan reports no disclosures.

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