CASE REVIEW: DISCUSSION

A Patient With Progressive Weakness and Cramping of Right Arm and Both Legs

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The following is a discussion of the case presented on pages e85-e88 of this issue.

A progressive disease with weakness and cramping of limbs without sensory loss in an adult is a disconcerting picture. Even without upper motor signs, this presentation raises the suspicion of motor neuron disease, such as amyotrophic lateral sclerosis (ALS), with its very poor prognosis. Based on our patient’s history and results of the neurologic examination, the differential diagnoses included anterior horn disease such as the hyporeflexive variant of ALS sometimes called progressive muscular atrophy (PMA), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), and vasculitic neuropathy.

Electromyography/nerve conduction study (EMG/NCS) is an important diagnostic tool for accurate diagnosis of peripheral nerve diseases, including anterior horn disease such as the hyporeflexive variant of ALS sometimes called progressive muscular atrophy (PMA), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), and vasculitic neuropathy.

In our case, EMG/NCS findings excluded ALS and CIDP and found evidence of a multifocal, mostly demyelinating peripheral neuropathy affecting the motor fibers and sparing the sensory fibers. Thus, with the history and examination results included, the picture fit the syndrome of MMN.

ALS was one of the considerable possible diagnoses after the first examination. Asymmetric progressive limb weakness, muscle cramps, fasciculations of muscles, muscle wasting, and normal sensory examination were suggestive of ALS. Against ALS was the lack of bulbar symptoms, although this can occur late in the course when the disease starts in the extremities. The multifocal demyelinating pattern of EMG/NCS eliminated ALS.

CIDP was another possible diagnosis in our case. The presence of hyporeflexia, and progressive limbs weakness for almost 1 year are consistent with CIDP. A normal sensory examination result, asymmetric muscle weakness with considerable muscle wasting, distal muscle involvement, and normal sensory nerve conduction studies were against CIDP. For a diagnosis of CIDP, the following features should be encountered: the progression of symptoms for at least 2 months, predominantly motor...
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symptoms, symmetrical involvement of arms and legs, proximal muscle involvement along with distal muscles, reduction or absence of deep tendon reflexes, elevation of cerebrospinal fluid (CSF) protein without pleocytosis, and nerve conduction evidence of a primary demyelinating neuropathy.3

MMN is a rare peripheral nerve disorder with a low prevalence, estimated at 1 to 2 per 100,000 individuals.4 The male to female ratio is about 2.5:1.7 and mostly affects men in their fourth and fifth decades.5 MMN usually presents as a lower motor neuron syndrome with asymmetric limb weakness and cramps, usually in the single nerve distributions in the upper limbs. As opposed to CIDP, MMN is slowly progressive, does not remit spontaneously, and (although occasionally accompanied by mild sensory symptoms) does not demonstrate sensory signs. High levels of circulating polyclonal IgM anti-GM1 are sometimes detected.6,7 In our case the patient tested negative for anti-GM1 antibodies.

The clinical diagnostic criteria for MMN are published8 and include the following: 1) Weakness without objective sensory loss in the territories of 2 or more nerves; 2) During the early stages of symptomatic weakness, the historical or physical finding of diffuse, symmetric weakness excludes multifocal motor neuropathy; 3) Definite conduction block is present in 2 or more nerves outside of common entrapment sites; 4) Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block; and 5) Absence of pyramidal signs including hypertonia, clonus, Babinski signs, and pseudobulbar palsy.

Electrodiagnostic Findings

EMG/NCS is the most important diagnostic tool in MMN. The critical electrodiagnostic finding of MMN is persistent, multifocal, partial conduction blocks (CB) of motor axons outside the common sites of nerve entrapment.9 CB is detected in the presence of lower compound muscle action potential (CMAP) amplitude or area on electrical stimulation of a nerve at a proximal site, compared with a distal site. In our case, there were conduction blocks in the right ulnar motor nerve (76% CBs) and bilateral tibial motor nerves (82% CBs in the left tibial motor nerve, 55% CBs in the right tibial motor nerve).

In MMN, nerve conduction velocity is usually significantly diminished across the small regions with CB, suggesting demyelination, though it may be normal or diminished only slightly in noninvolved segments.10 Other features of demyelination, such as prolonged distal CMAP latencies and prolonged or absent F waves, may be present in motor NCS. All these findings help in confirming the demyelinating process in MMN.9,11 In our case, distal latencies were prolonged, the ulnar and left tibial F waves were absent, and the right tibial nerve was prolonged.

Sensory NCS results are generally within normal limits or only minimally affected in MMN.11 Needle EMG shows reduced motor unit action potential (MUAP) recruitment in clinically weak muscles with preserved bulk; fasciculation potentials may be detected. Fibrillation potentials and positive sharp waves may be present in the case of secondary axonal loss, when muscle wasting may also be clinically evident.10 In our case, there were active and chronic denervation findings in needle EMG that might be due to secondary axonal loss.

Treatment

Steroids and Plasma Exchange

Even with high doses, steroid intravenous (IV) administrations11 are unsuccessful in the vast majority of patients with MMN.12,13 Around 20% of these cases have been reported to worsen significantly while on steroid therapy.14 Plasma exchange, immunoabsorption, and CSF filtration are similarly unsuccessful in most reported patients with MMN and only slightly effective in a few cases.15,16

IV Immunoglobin

The first successful trial of IV immunoglobulin (IVIg) in patients with MMN was around early 1990. After therapy with high-dose IVIg, the patients with MMN had significant improvement.17 Since then, this therapy has been used widely in MMN.

Several randomized controlled trials have confirmed the efficacy of IVIg in treating MMN.18,20 In these trials, patients usually had rapid improvement within 1 week of IVIg treatment; however, its effect lasted only a few weeks in a vast majority of the patients. Periodic IVIg maintenance infusions must be continued for a long time. Stabilization of symptoms is provided in a minority of
patients after a single or a few courses of IVIg, the majority requiring long-term periodic courses because of worsening after 3 to 8 weeks.\textsuperscript{21}

Léger and colleagues\textsuperscript{22} recently performed a retrospective study regarding short- and long-term responses to IVIg therapy in 40 patients with MMN. They demonstrated that only 22\% of patients in their cohort were able to stop IVIg therapy after a few months or years without clinical worsening, but that the majority needed periodic IVIg infusions to maintain remission. This study failed to demonstrate any predictive factors for IVIg response and showed a 70\% response rate to IVIg in treatment-naïve patients.\textsuperscript{22}

The IVIg therapy in patients with MMN is generally initiated at the standard dose of 2 g/kg on 2 to 5 consecutive days. Maintenance infusion needs to be continued in these patients, ranging from 0.4 g/kg once a week, or 1 to 2 g/kg on 2 to 5 days monthly or before or at the beginning of clinical worsening, which usually occurs around 3 to 8 weeks.\textsuperscript{23}

Our patient has undergone 4 courses with IVIg and has noted a dramatic improvement in his symptoms. He feels that his strength has improved considerably. The only limb that remained weak was his right leg, in which he had a partial foot drop, but this also improved significantly. His weakness in the right arm has resolved. His right intrinsic hand muscle strength has improved from 3/5 to 5/5. He initially had 0/5 strength in right foot dorsiflexion that was improved to 3/5.

\textit{Rituximab}

Rituximab is a monoclonal antibody directed against the surface marker CD20 of activated B-cells. Stieglbauer and colleagues\textsuperscript{24} recently reported on 3 patients with MMN, with declining response to IVIg therapy, who improved after rituximab monotherapy. Further trials are needed to determine if rituximab may be a viable alternative to IVIg.

\textbf{Conclusions}

MMN is a diagnostic challenge that generally can be resolved with careful neurophysiologic studies demonstrating CB and other features just discussed. Anti-GM1 antibodies may be helpful but alone are nondiagnostic and often negative. The long-term follow-up studies\textsuperscript{23,25} of MMN treatment demonstrate that even though periodic IVIg therapy improves muscle strength and disability, it does not ultimately cure MMN. Further investigations are warranted to develop new treatment modalities that can be used alone or in combination with IVIg.

\textbf{References}


\textbf{Main Points}

- Electromyography and nerve conduction studies are important diagnostic tools for the accurate diagnosis of peripheral nerve diseases, including anterior horn diseases.
- In multifocal motor neuropathy (MMN), nerve conduction velocity is usually significantly diminished across the small regions with conduction blocks, suggesting demyelination, though it may be normal or diminished only slightly in noninvolved segments.
- Treatment with steroids and plasma exchange has been largely unsuccessful. Several randomized controlled trials have confirmed the efficacy of intravenous immunoglobulin (IVIg) in treating MMN; however, its effects are usually short-lived and in a majority of patients maintenance infusions must be continued for a long time.
- Further trials may determine if rituximab monotherapy is a viable alternative to IVIg.