Title: Focal Amyotrophy in Multiple Sclerosis

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No funding disclosures

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Running title: Focal Amyotrophy in MS
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ABSTRACT

Introduction: The assumption that multiple sclerosis (MS) is purely a white matter disease has been challenged in recent years by observations of axonal damage and neuronal loss in gray matter of the cortex, subcortex, and spinal cord. Methods and Results: We report the case of a 71 year old man with primary progressive MS and longstanding right arm weakness who presented with intermittent right arm pain. Neurological examination showed atrophy, weakness, and hyporeflexia, and electromyography (EMG) showed acute and chronic partial denervation in multiple segments of the right arm. Magnetic resonance imaging (MRI) demonstrated asymmetric volume loss and increased T2 signal in the right anterior spinal cord from C3 to C7, with no evidence of nerve root compression. Discussion: We conclude that the lower motor neuron involvement of his right arm was caused by MS with involvement of either the anterior horn cells or the intraspinal motor nerve roots.

Key words: amyotrophy, spinal cord, multiple sclerosis, axonal, demyelination.
INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated inflammatory disease of the central nervous system. Although demyelination is the primary pathological process, inflammation is not restricted to the white matter alone. It can extend into the gray matter, as demonstrated by immunohistopathology, which also shows decreased neuronal density, suggesting neuronal loss, in the affected area. Likewise, magnetic resonance spectroscopy has shown a decrease in N-acetyl-aspartate (NAA), creatine, and NAA/creatine ratio in occipito-parietal cortical gray matter, suggesting a reduction of neuronal and axonal density. More recently there is evidence to suggest spinal cord neuronal loss, as discussed below. Here we report the case of a patient with MS who had clinical, imaging, and electromyographic evidence of focal spinal motor neuron involvement.

CASE REPORT

A 71-year-old right-handed man presented at age 50 years with a 1-year history of right lower extremity weakness. For the preceding 10 years he had experienced multiple transient neurological symptoms including right leg paresthesias and episodic vertigo. A year prior to presentation he noted clumsiness of the right leg when walking. A few months later he noted weakness of the right hand followed by urinary precipitancy and dysarthria. On neurological exam, he was noted to have cerebellar dysarthria. There was horizontal and vertical nystagmus.
An upper motor neuron pattern of weakness of the right upper extremity was noted along with astereognosis. Deep tendon reflexes were normal, but there were bilateral Babinski signs. There was cerebellar ataxia of the right lower extremity. Cerebrospinal fluid (CSF) analysis showed elevated protein, normal IgG index, and no oligoclonal bands. A serum antibody test against aquaporin-4 (AQP4) was negative as were anti-SSA and anti-SSB antibodies. Antinuclear antibody was mildly elevated at 8 IU/ml (reference <7.5 IU/ml). Magnetic resonance imaging (MRI) revealed atrophy of the brain, including corpus callosum, multiple foci of increased signal intensity in the periventricular white matter, and a small focus in the left anterior pons. Given the clinical history, neurological exam, and imaging findings, he was given a diagnosis of multiple sclerosis. The weakness worsened slowly, and he became wheelchair-bound at age 58.

The neurological examination remained largely unchanged over the following decade. At age 71 he developed severe, intermittent, electric shock-like pains in his right arm. He reported no new sensory or motor deficits in the right arm, which was chronically weak. He denied dysarthria, dysphagia, or shortness of breath.

General physical examination was unremarkable. On neurologic examination, the mental state was normal. Cranial nerves were intact with no facial weakness or tongue atrophy. Neck extensors and flexors had full power. There was moderate atrophy of right hand muscles. Tone was normal in the arms and left leg and increased in the right leg. There were no fasciculations. There was mild weakness of the right deltoid, biceps, and triceps muscles, moderate weakness of wrist extensors and flexors, and severe weakness of finger extensors, interossei, and abductor pollicis brevis muscles. There was full strength in the left arm and in both legs. Deep tendon reflexes were hypoactive in the right arm. He had hyperreflexia of the left arm and right leg but
normal reflexes in the left leg. He was unable to walk because of spasticity but was able to transfer independently. On coordination testing, repetitive movements of the right fingers and toes were slow. Sensory examination revealed intact light touch perception but a patchy loss of pain sensation in the entire right arm in a circumferential distribution. There was decreased vibration sense and proprioception in the right hand up to the wrist.

Nerve conduction studies of the right arm revealed normal median and ulnar motor and sensory responses. The right median compound muscle action potential (CMAP) amplitude, although within normal limits for age, was 30% smaller than the left. On electromyography, there were chronic repetitive discharges and fibrillation potentials in the right triceps and deltoid muscles and reduced recruitment of long duration motor unit action potentials (MUAPs) in the right abductor pollicis brevis, first dorsal interosseous, extensor indicis proprius, and triceps muscles. Needle electromyography of the left arm, right leg, and thoracic paraspinal muscles was normal. Cervical paraspinal muscles were not studied. There was a suprasegmental pattern for MUAP activation in all muscles sampled. In summary, the study revealed acute and chronic partial denervation with re-innervation in multiple muscles of the right arm supplied by different nerves and roots, as seen either in anterior horn cell disease or in multiple cervical radiculopathies.

MRI of the cervical spine demonstrated myelomalacia from C3 to C7, most severe at C4 and C5, with asymmetric volume loss and T2 prolongation affecting the right anterior quadrant of the spinal cord. There was no neuroforaminal narrowing (Figures 1 and 2). The findings were unchanged from an MRI performed 5 years earlier. MRI of the brain revealed numerous foci of T2 prolongation in the periventricular white matter without enhancement. The episodic right arm
pain was thought to be a paroxysmal symptom of spinal cord MS and responded to treatment with carbamazepine.

DISCUSSION

This patient presented with paroxysmal right arm pain that responded to carbamazepine treatment. This phenomenon has been described in demyelinating diseases such as MS and NMO and is thought to arise from ephaptic discharges originating in demyelinated tracts.\(^3,4\) Some of the clinical features in this patient resemble those reported by Katz and Ropper\(^5\) as idiopathic progressive myelopathy. Their 9 patients presented after age 40 with pain and weakness of the extremities. They had flaccid weakness, atrophy, and areflexia of the upper extremities with electrodiagnostic evidence of denervation. CSF analysis revealed absent oligoclonal bands and elevated protein. MRI showed an extensive spinal cord abnormality consisting of a central T2 hyperintensity and swelling with subsequent development of cord atrophy. The authors attributed this syndrome to NMO spectrum disease, although the AQP4 antibody test was not then available. We considered the diagnosis of NMO in our patient, but we thought it unlikely, given the absence of optic nerve involvement and the presence of cerebellar and cerebral signs and symptoms. In addition, the negative serology including anti-AQP4, anti-SSA, and anti-SSB antibodies, and a clinical course characterized by slow progression rather than punctuated attacks, distinguish our patient from that case series.

We attribute the lower motor neuron findings in the right upper extremity to focal involvement of the anterior spinal cord as demonstrated by cervical cord imaging. There was no evidence of
disease of the extraspinal nerve roots, and electrodiagnostic studies did not reveal an underlying plexopathy or neuropathy. There was no evidence of widespread denervation changes to suggest a diagnosis of amyotrophic lateral sclerosis (ALS), and the motor deficits had not changed for 10 years. The initial symptoms that led to the diagnosis of MS were in the right arm, which remained the region most severely affected by the disease. In nonambulatory patients with longstanding MS, the extent of disability has been shown to correlate with spinal cord axonal loss and a reduced level of the neuronal marker NAA.6

Shefner and colleagues noted that focal limb muscle atrophy in MS was accompanied by electrodiagnostic evidence of denervation, suggesting pathology at either the nerve root or the anterior horn cell level.7 They attributed the denervation to demyelination of the ventral root exit zone, although this was not visible on MRI. However, since then there has been a growing body of evidence demonstrating anterior horn cell loss, which could explain these findings.

Dive and Eron8 reported a 24 year old woman with left hand amyotrophy for 3 months due to a gadolinium-enhancing lesion of the left anterior cord at C6-7. CSF contained oligoclonal bands, and electrodiagnostic studies pointed to an anterior horn localization. She recovered almost completely following treatment with corticosteroids and interferon-beta. Using morphometric analysis, Gilmore et al found a decrease in the absolute number of anterior horn neurons in cervical and thoracic levels of the spinal cord in autopsy material from patients with multiple sclerosis.9 Schirmer et al found that this neuronal loss occurred early in developing lesions and did not increase with lesion stage or disease duration.10 They were able to demonstrate evidence for retrograde neuronal demise of the ventral spinal neurons. The C-Jun gene, which is
upregulated in acute neuronal injury, was demonstrated in neurons in and around active
demyelinating lesions, and the spinal neuron morphology was felt to be consistent with
retrograde chromatolysis. A process of regeneration was identified by the presence of
immunoreactivity for GAP43, a protein thought to play a role in axonal regeneration and
synaptogenesis.

Finally, Vogt et al demonstrated a 20%-30% reduction of CMAP amplitudes and a 38%
reduction of estimated motor unit numbers in an unselected group of 69 MS patients. This drop
in mean CMAP amplitude was greater in patients with reduced walking distance [mean
Expanded Disability Status Scale (EDSS) ≥4] compared to those without gait impairment
(EDSS≤3.5). There was no significant difference in the conduction velocities, distal motor
latency, or sensory nerve action potentials. Postmortem studies of 9 MS patients using stereology
showed a 75% loss of thoracic and lumbar motor neurons. Spinal motor neurons in chronic
active MS showed signs of apoptosis and were often surrounded by CD3+ T cells. Interestingly,
lamina 5 and 6 of the cerebral cortex showed only a slight decrease in neuronal cell density,
implying that the neuronal cell loss was a specific feature of the spinal cord.

In summary, there is now abundant evidence for spinal motor neuron degeneration in MS,
although this is not usually as obvious clinically as in our patient. Whether the neuronal
degeneration is due to a direct attack on neurons or is a retrograde process secondary to axonal
damage within the spinal cord, is still uncertain.
ABBREVIATIONS

ALS – amyotrophic lateral sclerosis

CMAP – compound muscle action potential

CSF – cerebrospinal fluid

EDSS – expanded disability status scale

EMG – electromyography

MRI – magnetic resonance imaging

MS – multiple sclerosis

MUAP – motor unit action potential

NAA - N-acetyl-aspartate
REFERENCES


Committee for Treatment and Research in Multiple Sclerosis. Dusseldorf, Germany 2009.


FIGURE LEGENDS

**Figure 1:** Sagittal T2-weighted image (parasagittal, right of midline) demonstrating severe atrophy of the cervical cord from C3 to C5. There is slight motion degradation of the image.

**Figure 2:** Multiple sequential axial T2-weighted images of the cervical cord demonstrating severe, asymmetric atrophy of the right hemicord and increased T2 signal (white arrows) involving the right ventral cord. Of note, the neural foramina (black arrows) remain patent.
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230x349mm (300 x 300 DPI)
Figure 2: Multiple sequential axial T2-weighted images of the cervical cord demonstrating severe, asymmetric atrophy of the right hemicord and increased T2 signal (white arrows) involving the right ventral cord. Of note, the neural foramina (black arrows) remain patent.