Patterns of Weakness, Classification of Motor Neuron Disease, and Clinical Diagnosis of Sporadic Amyotrophic Lateral Sclerosis

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KEYWORDS

• Motor neuron disease • Upper motor neuron • Lower motor neuron
• Amyotrophic lateral sclerosis • Lou Gehrig disease

KEY POINTS

- Patterns of weakness can be useful when approaching a patient with suspected motor neuron disease (MND).
- MNDs exist on a spectrum: pure lower motor neuron ↔ mixed upper and lower motor neuron ↔ pure upper motor neuron.
- Amyotrophic lateral sclerosis (ALS) is a progressive mixed upper and lower MND that is most commonly sporadic and invariably fatal.
- A better understanding of the genetics and pathophysiology of heritable ALS may yield insights into possible therapies for sporadic ALS.

PATTERNS OF WEAKNESS

Neuropathic disorders can be broadly divided into disorders affecting the peripheral nerve processes (neuropathy) or nerve cell body (neuronopathy), can be inherited or acquired, and have different clinical courses.[1] MNDs are neuronopathies. When

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approaching a patient with a suspected neuropathy or neuronopathy, there are several key questions that can help further categorize the disorder:

- Which parts of the nervous system are involved: motor, sensory, or autonomic or a combination of more than 1 system?
- Where is the weakness (proximal, distal, or both) and is it symmetric or asymmetric?
- If there is sensory involvement, is there pain or proprioceptive loss?
- Over what time frame did symptoms evolve: acute (<4 weeks) or subacute (4–8 weeks) or is it chronic?
- Is there a family history of a similar disorder?
- If there is motor involvement, is it upper motor neuron, lower motor neuron, or both?

The neuropathic disorders can be confusing to a clinician first encountering them but several key patterns of involvement can help lead to the proper diagnosis (**Table 1**). For a full description of the neuropathic patterns (NP), readers are referred to Barohn and Amato.[1] Some of the myopathic patterns, including myopathy pattern (MP) 6 (neck extensor weakness) and MP7 (tongue, pharyngeal, or diaphragm), described previously, also overlap with MND.[2]

MNDs are typically motor syndromes (sensory sparing) that show insidious onset; are chronically progressive; can be distal, proximal, or mixed; and can have different combinations of upper and lower motor neuron findings. They can be inherited or sporadic. There several neuropathic patterns seen in the MNDs.

Asymmetric Distal Weakness Without Sensory Loss (NP5)

If a patient comes in with asymmetric onset of distal weakness or muscle wasting and upper motor neuron findings on examination (brisk reflexes with spread to other regions, Babinski sign, Hoffmann reflex, or increased tone), ALS is a main consideration, in particular, if the onset was insidious and the weakness is painless. If there are only upper motor neuron findings on examination, then primary lateral sclerosis (PLS) needs to be considered in the differential diagnosis (see the article by Statland and colleagues[3]). If a patient only has lower motor neuron findings (muscle wasting or fasciculations), then the differential is broader and includes a motor neuron disorder, like progressive muscular atrophy (PMA) (see the article by Liewluck and colleagues[4]); acquired diseases of motor neurons, like multifocal motor neuropathy or multifocal acquired motor axonopathy; or para-infectious complications (polio-like illness). As the disease progresses, distal weakness may become symmetric and progress proximally and reflexes may be attenuated as can be seen with MP2 or NP7.[2]

Symmetric Weakness Without Sensory Loss (NP7)

If weakness is proximal more than distal or both, then spinal muscular atrophy (SMA) and PMA are considerations. If weakness only includes upper motor neuron signs, then PLS is a consideration. If the weakness is distal only, then other heritable conditions, like distal SMA, hereditary motor neuropathy, and Charcot-Marie-Tooth disease become considerations. Sensory loss on examination in NP7 is evident, however, for Charcot-Marie-Tooth disease despite the absence of sensory symptoms, but when sensory symptoms are present, it is classified as NP2.

Focal Midline Proximal Symmetric (NP8)

If the neck and trunk are prominently involved, ALS is the main consideration, also known as MP6. If the onset is mostly bulbar, as in MP7, then ALS and variants that