

Clinical Mimickers of Amyotrophic Lateral Sclerosis-Conditions We Cannot Afford to Miss

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Abstract

Giving a diagnosis of amyotrophic lateral sclerosis to a patient is akin to handing out a death certificate. However, not all patients presenting with the classical dysphagia, wasting, and weakness may have motor neuron diseases. In these cases, it is extremely important not to miss little cues which can suggest an alternative diagnosis and in many cases a lease of life in terms of a treatment option. In this review, we consider some clinical scenarios that can present with the same symptom complex as diseases involving motor neurons but have a different anatomical or etiopathological basis and in many cases even a therapeutic option.

Keywords: Amyotrophic lateral sclerosis, lower motor neuron, mimickers, upper motor neuron

INTRODUCTION

Motor neuron disease is an adult-onset progressive neurodegenerative disorder involving motor neurons of both cortex and spinal cord. Both sporadic and familial forms are well-known, and phenotypic involvement is that of progressive involvement of upper motor neuron (UMN) as well as lower motor neuron (LMN) systems and is associated with high morbidity and mortality. It is thus imperative to consider all differentials with similar manifestations before diagnosing a disease as motor neuron disease.

EPIDEMIOLOGY

The average incidence of motor neuron diseases (MND) has grown from the sixties and seventies by up to 46% and now stands at about 1.89 per 100,000/year. The increased incidence could reflect refined El Escorial criteria as well as increased life expectancy and accuracy of death certificate collection.[1]

However, the diagnosis of amyotrophic lateral sclerosis (ALS) is seen to be more accurate in up to 95% of cases with bilateral presentation but fell to almost 38% in patients with unilateral (hemiparetic) or pseudopolyneuritic forms.[2] Population-based studies have shown that almost 10% of patients diagnosed with ALS have had another disease.[3] Hence there is a great need to discuss the differentials and rule out alternate pathology. Here, we approach the mimics depending on the pattern of involvement.

LOWER MOTOR NEURON ONLY SIGNS

Benign fasciculation syndrome

Benign fasciculation syndrome is a commonly encountered differential for motor neuron disorders. However, exercise, anxiety, thyrotoxicosis, excessive caffeine intake, and alcohol may all cause fasciculations and need to be ruled out. In only a small subset of patients who progress from fasciculations to motor wasting and signs of MND, an abrupt onset and widespread distribution are noted. Calf fasciculations usually signify a guarded prognosis compared to abdominal fasciculations. Moreover, fasciculation waveforms in ALS are usually of shorter duration with the greater number of turns and firing rate compared to benign fasciculations. Double fasciculations and increased firing rate usually signify LMN involvement in ALS.[4]

Multifocal motor neuropathy with conduction block

Multifocal motor neuropathy with conduction block (MMNCB) with a prevalence of around 0.6/100 000 is about ten times rarer than MND and has a younger age of onset as a pure motor neuropathy characterized by slowly progressive, asymmetrical, and distal weakness with minimal wasting and with a male predominance. Wrist or finger drop is common initial symptoms and mimic anterior horn cell involvement. Sensory involvement is characteristically absent. Reflexes are usually lost but can be retained, they can be brisk in up to 20%. Cranial nerves are spared. Bulbar and respiratory involvement is usually absent. The most significant finding in MMNCB is the presence of conduction blocks on nerve conduction studies. However, conduction blocks may be absent in some due to their dependence on activity. Sensitive techniques such as transcranial magnetic stimulation, triple stimulation technique, and transcutaneous cervical root stimulation technique are useful to elicit conduction blocks when not evident. It is important to rule this condition out in view of the therapeutic potential with intravenous immunoglobulin (IVIg) in affected patients.[5]

Neuralgic amyotrophy

Parsonage–Turner syndrome (neuralgic amyotrophy or idiopathic brachial neuritis) is a disorder of unknown etiology occurring most commonly between the third and seventh decades of life. It typically presents with severe unilateral neck, shoulder, or arm pain in the absence of trauma, followed by weeks of progressive upper limb weakness and muscle wasting, often involving multiple nerve root territories. Pain maybe absent in up to 5% of cases.[6] Lower limb involvement is much less common. Often, a viral illness or vaccination may precede the condition, but 10% of cases show a family history, with half of these linked to a point mutation or duplication in the SEPT9 gene, in which case the clinical picture is one of the repeated episodes of pain followed by weakness and sensory loss.[7] Hereditary neuralgic amyotrophy is a closer differential with the gradual affliction of brachial plexus over months to years with slowly progressive painless weakness and wasting of the affected segments and relatively mild sensory findings. Nerve conduction studies show the involvement of sensory as well as motor nerves with features of demyelination, and electromyographic (EMG) studies show neurogenic potentials in the affected limb.[8]

Spinobulbar muscular atrophy

An X-linked polyglutamine genetic disorder caused by cytosine-adenine-guanine trinucleotide repeats in the androgen receptor gene presents in males in their third or fourth decades with atrophy and weakness of bulbar, facial, and limb-girdle muscles indicating involvement of brainstem and spinal cord and orolingual fasciculations with signs of endocrine dysfunction as diabetes mellitus, gynecomastia, and testicular atrophy. Involvement is usually symmetrical and sensory involvement maybe seen subclinically. Genetic test is diagnostic. There is no effective treatment at present.[3]

Motor-predominant chronic inflammatory demyelinating polyradiculoneuropathy

A motor-predominant variant may account for up to 33% of all cases of chronic inflammatory demyelinating polyradiculoneuropathy. It is distinguished by a relapsing and remitting course and is a predominantly symmetrical weakness with a predilection for upper limbs, no wasting, clear demyelination electrophysiologically, and good response to IVIg therapy.[9]

Inclusion body myositis

Inclusion body myositis (IBM), one of the closest differentials for ALS, is a slowly progressive painless myopathy with a characteristic predilection for asymmetric wasting of the wrist flexors, finger flexors, and quadriceps muscles. The involvement of these muscles favors IBM over anterior horn cell disease. Another common feature is a relative absence of cramps and normal or mildly elevated serum creatine kinase levels (<10 times the normal limit). Typically, patients are over 50 years, with 3:1 male-to-female ratio. The combination of active or overactive reflexes in weak, wasted limbs has been considered by some indicative of ALS. IBM can also present with exaggerated reflexes in up to 5% of cases, thus confounding the diagnosis.[\[10\]](#)

Up to 13% of patients with IBM can be misdiagnosed initially as motor neuron disease. Visible fasciculations in tongue and limb muscles are suggestive of an anterior horn cell disorder, which have not been reported. However, EMG fasciculation potentials may be observed in up to 10%–40%. On the other hand, dysphagia without significant dysarthria occurs in up to 65% of the patients with IBM and can be debilitating.

EMG may be misleading in IBM as it may show neurogenic motor unit potentials, fibrillation potentials, positive sharp waves, and fasciculation potentials. However, similar potentials can be seen in chronic myogenic disease, making a quantitative analysis of both polyphasic and simple units essential in such chronic muscle diseases. The quantitative motor unit analysis in IBM gave evidence of a myogenic disorder (short duration) when only simple units were analyzed. Quantitative muscle of the quadriceps muscle and IBM-functional rating scale were the most sensitive measures of disease progression. Muscle biopsy is diagnostic and along with quantitative EMG should be considered in patients with presumed MND if there is a long history of preferential involvement of the above-mentioned muscle groups.[\[11,12\]](#)

POLYMYOSITIS AND OTHER MUSCLE DISORDERS MIMICKING ANTERIOR HORN CELL DISORDER

Bulbar dysfunction is a symptom common to both polymyositis and ALS. However, dysphagia is a prominent feature that separates polymyositis from ALS in which dysarthria is the main complaint. Dysphagia usually occurs due to dysfunction of the pharyngeal muscles and can also be seen in other conditions such as stroke, craniovertebral junction defects, and the Miller Fisher variant of Guillain-Barre syndrome. However, the presence of LMN signs in addition to the lower motor ones will favor anterior horn cell pathology.[\[13\]](#)

Oculopharyngeal muscular dystrophy may simulate bulbar-onset ALS, but in contrast to ALS, there is an associated involvement of ocular muscles. In those rare cases that present with bulbar manifestations and subtle or no extraocular involvement, a muscle biopsy may be required to differentiate it from MND.

Isolated neck extensor myopathy occurs in older persons with dropped head extensor weakness. It is associated with the signs of active denervation in cervical paraspinal muscles similar to ALS, but the weakness does not spread to other regions.

Radiation-induced radiculopathy

A pure lower motor syndrome has been described due to radiotherapy to the pelvis and para-aortic lymph nodes given for testicular and gynecological tumors after highly variable periods of latency. The latency to developing symptoms may be decades. The pathogenesis has been deliberated on widely, with some suggesting nerve compression by indirect extensive radiation-induced fibrosis and the rest suggesting vasculopathy as the causative mechanism. Spongy demyelination and axonal swelling, followed by atrophy, vascular damage, and plasma cell infiltrates are the histopathological changes. Usually, the condition is very slowly progressive but may lead to cumulative significant disability with bladder and bowel involvement. Pain may be present in up to 50% of cases. It is usually bilateral and asymmetric with the initial unilateral damage, and the sensory signs and paresthesia are absent or noted very late. Similarly, the brachial plexus involvement, following breast cancer, usually occurs with a more recent history of exposure and is more easily differentiated from MND by the presence of pain; however, it may not always be present. Nerve conduction studies in the early stages may show features of demyelinating conduction blocks. EMG studies in radiation injury show spontaneous activity in the form of myokymic discharges and indicate a dismal prognosis.[\[14\]](#)

Myasthenia gravis

Myasthenia gravis (MG) is the most common disorder of neuromuscular transmission with fluctuating weakness in the ocular, bulbar, limb, and respiratory muscles. About 15% of the patients present with bulbar symptoms. Presentation with isolated slowly progressive dysarthria with or without dysphagia makes differentiation of MG diagnostically challenging. In these patients, it is wiser to rule out structural pathologies by imaging and other modalities.

In myasthenia patients, symptoms have a fatigable component, whereas in ALS, the dysarthria and dysphagia are typically progressive and nonfluctuating. However, up to 10%–15% of patients in the early part of the disease course may give a history of fluctuation or worsening after prolonged talking or at the end of the day. It is important to differentiate the “flaccid,” ‘nasal’ LMN quality of speech in MG versus the “strangled” speech quality of ALS with a combination of spastic and flaccid qualities.

Whereas tongue atrophy points more to ALS, fasciculations may additionally be seen in muscle-specific receptor tyrosine kinase-positive patients.^[15] Similarly, while dysphagia is a presenting symptom in both conditions, a difficulty in clearing the throat is a complaint in ALS, whereas regurgitation through the nose occurs in MG due to palatal weakness. Head drop can be the presenting symptom in ALS or MG. It can also be the presenting symptom in isolated neck extensor myopathy. Generally speaking, when head drop is seen in MG, other signs or symptoms, such as ptosis, extraocular muscle weakness, facial weakness, or fatigable limb weakness, usually lead one to the correct diagnosis.

Wasting in ALS is out of proportion to weakness, to the extent that they may not even complain of weakness. Diplopia is another clinical sign that can help to differentiate anterior horn cell pathology from neuromuscular junction one.^[16] Fatiguing maneuvers may be needed to elicit weakness in MG. Limb weakness in ALS can occur in any muscle group, but the most common presentation of limb weakness in ALS is asymmetric distal limb weakness, in the form of wasting in ulnar-innervated segments or with finger/wrist drop or even foot drop.

Repetitive nerve stimulation (RNS) studies and single-fiber EMG (SFEMG) are the electrodiagnostic tests used to confirm the presence of a defect in neuromuscular transmission in MG. However, RNS and SFEMG abnormalities are relatively nonspecific. Other primary disorders affecting the nerve or motor neuron and even muscle may show abnormalities on RNS and/or SFEMG that may be mistaken for MG. For example, abnormal decremental responses on RNS and increased jitter on SFEMG may both be present in patients with motor neuron disease. In fact, SFEMG can be abnormal in all cases of ALS, making it one of the most sensitive tools for diagnosis of ALS, with progressive denervation and reinnervation causing immature collateral sprouts which can cause increased jitter, blocking percentage, and fiber density.^[17] In MG, however, the conventional NCS and EMG studies are normal. Increased jitter on SFEMG is associated with increased fiber density in ALS, while fiber density will be normal in MG.^[18]

A clinical response to edrophonium or to treatment with pyridostigmine is supportive evidence in favor of the diagnosis of MG. However, any condition causing impaired neuromuscular transmission has the potential to respond positively to cholinesterase inhibitors. This includes patients with ALS particularly in the early phases due to active re-innervation and de-innervation. However, this response is relatively short-lived and typically wears off as the disease progresses.

UPPER MOTOR NEURON ONLY SIGNS

Multiple sclerosis

In multiple sclerosis, both UMN and LMN involvement may be seen in the setting of plaque formation at root exit zones, combined with central nervous system lesions. Primary progressive multiple sclerosis which may occur in 15% of the cases with multiple sclerosis is the subtype with a controversial presentation and may mimic primary demyelination, especially the primary lateral sclerosis subtype. It is more common in men and the age at symptom onset is older (fifth decade). Oligoclonal bands may sometimes be seen in ALS as well.^[19]

Hereditary spastic paraparesis

Hereditary spastic paraparesis is a heterogeneous group of disorders characterized by very slowly progressive paraplegia, which can sometimes involve dorsal column, sphincter dysfunction, and the upper limbs. They can also present with ataxia or dementia, but they do not include the often severe corticobulbar or evidence of LMN involvement seen in ALS. The presence of a family history is a major clue to hereditary spastic paraparesis, and nearly 40% of such cases will have mutations in the SPAST gene.[\[20\]](#)

Metabolic myelopathies

Vitamin B12 and copper deficiencies are well-recognized causes of slowly progressive myelopathy but typically have sensory complaints in the form of paresthesias, tingling, and posterior column involvement. It is rare for these conditions to be construed for anterior horn cell involvement.

Adrenomyeloneuropathy presents with spastic paraparesis, areflexia, sphincter disturbance, and sensory loss. It is a peroxisomal disorder caused by a defect in beta-oxidation of very long-chain fatty acids, presenting in their third or fourth decades of life. Increased plasma levels of very long-chain fatty acids make the diagnosis. There are frequently no abnormal MRI findings, although occasionally secondary Wallerian degeneration results in hyperintense cerebral corticospinal tracts. There is no effective treatment at present. Family history suggestive of X-linked inheritance with features of adrenal insufficiency, age of onset, and sensory complaints point toward an alternate diagnosis to ALS.

MIXED LOWER MOTOR NEURON AND UPPER MOTOR NEURON SIGNS

Adult polyglucosan disease

Adult polyglucosan body disease is rare glycogenosis manifesting as a late-onset, slowly progressive disorder of both UMN and LMN, like ALS, with a mean age of onset between fifth and sixth decades. Early bladder involvement may not be present in all patients, and cognitive decline may appear later.[\[3\]](#) It is caused due to mutations in glycogen-branching enzyme (GBE) gene and is commonly seen in Ashkenazi Jews but may even occur in other different populations. MRI of the brain may reveal diffuse white matter signal increase on T₂-weighted images (midbrain, medullary olives, dentate nuclei, cerebellar peduncles, and internal and external capsules, with vermian atrophy), and the diagnosis is confirmed by the findings of characteristic nonmembrane-bound periodic acid–Schiff-positive cytoplasmic polyglucosan bodies in axons and neural sheath cells in nerve biopsy. A high index of clinical suspicion is a must, especially since the age of onset is similar to ALS. The presence of prominent urinary complaints, sensory loss, and altered cognition is clues to an alternative diagnosis.[\[21\]](#)

Syringomyelia

Syringomyelia may present with atrophy and weakness in small muscles of the hand followed by entire limb with brisk DTRs, but a characteristic pattern of dissociated sensory loss typically occurs, and the disease progresses at a much slower rate in a usually younger patient than ALS.

Cervical myeloradiculopathy

The proximity of both UMN and LMN structures in the cervical spine makes degenerative myeloradiculopathy, an important diagnostic challenge in cases of suspected ALS. Moreover, pure motor syndromes and absent sphincter involvement are not uncommon in cervical spondylotic disease. Incidental spondylosis of the spine is highly prevalent among those with MND, given the mean age of onset of 65 years.[\[22\]](#) Emotionality and abnormal signs above the neck are clues to not make a misdiagnosis of cervical radiculopathy. Furthermore, the presence of fasciculations in the bulbar and lumbosacral areas is a clue to alternate diagnosis.

LMN-predominant upper limb presentations of MND frequently involve multiple myotomes, making cervical spine spondylotic polyradiculopathy an unlikely consideration. However, the characteristically slowly progressive, symmetrical LMN “flail arm” variant of MND (also known as brachial diplegia or “man-in-a-barrel” syndrome) is one subtype that can be mimicked by cervical spine pathology.

Third-A syndrome

Allgrove or “Four-A” syndrome is a rare autosomal recessive disorder that derives its name from the combination of achalasia, alacrimia, adrenal insufficiency, and amyotrophy.

Achalasia is present in 75% of patients and alacrimia is the most consistent clinical finding. Adrenal insufficiency may present later but within the first decade. In these patients, upper and LMN signs were the most frequent neurological manifestations with less common sensory impairment. Bulbospinal amyotrophy was reported in one patient with Triple-A syndrome. The upper limb amyotrophy, with a predominance on the ulnar side of the hands, resembles that of ALS, and bulbar sign and symptoms (tongue atrophy and fasciculation) have led to the misdiagnosis of bulbar ALS.[\[23\]](#) Thus, it should be considered as a rare differential diagnosis in patients with juvenile-onset ALS. In addition to the three possibly subclinical main symptoms of Triple-A syndrome, intellectual disability and dysautonomia may help to differentiate between ALS and Triple-A syndrome.

Other systemic diseases

Thyrotoxicosis may present with corticospinal tract signs (hyperreflexia), fasciculations, weight loss, and weakness. However, there usually are additional systemic signs such as heat intolerance, anxiety, tremor, tachycardia, and insomnia. Weakness may also be seen in hyperparathyroidism and mimic LMN onset ALS. There have been authors who have reported some correlation between hyperparathyroidism and MND, but no conclusive evidence has yet been established. Similarly, there have been reports of MND/ALS with aberrant calcium metabolism, but till date, no causal relationship has been established.[\[24\]](#)

Patients with hyperparathyroidism can present with B/L symmetrical proximal weakness along with brisk deep tendon reflexes with downgoing plantar response, in contrast to patients with ALS mainly present with asymmetrical predominant distal weakness. PHP may even present with bulbar paralysis and abnormal tongue movements in addition to muscle cramps. Main discriminating features for PHP are the presence of associated loss of pain and vibration sense in the glove and stocking areas, ataxia, decreased arm swing, poor memory, disorientation, emotional lability, personality change, anxiety, disorientation, and hallucination.

Infections

Human immunodeficiency virus (HIV) infection may also clinically mimic ALS. A retrospective review of 1700 cases of HIV-positive patients with neurological symptoms documented six cases presenting as an ALS-like syndrome. These developed distal motor weakness mimicking a monomelic amyotrophy that subacutely progressed regionally or assumed a symmetric distribution on more than one region. EMG was characteristic of motor neuron disease but no multifocal conduction block. Possible mechanisms are through neuronal infection, by secretion of a toxic viral substance, by inducing the immune system to secrete cytokines, or by inducing an autoimmune disease.[\[3\]](#)

Post-polio syndrome

Post-polio syndrome develops after a period of stability in a proportion of patients who have recovered from acute poliomyelitis. They present with new weakness and muscle atrophy, fatigue, and/or pain. The cause remains unclear and may be due to the degeneration of enlarged reinnervated motor units. The presence of only LMN signs with no evidence of UMN signs and previous history of poliomyelitis are important clues to differentiate with ALS.[\[25\]](#)

CONCLUSION

Although the essential diagnostic criteria of ALS are defined by the El Escorial criteria, there are still many misdiagnoses. Our mistakes in ALS diagnosis mainly relate to diagnostic difficulty and also to lack of skill and knowledge about MNDs. To reduce the misdiagnosis rate, enhanced knowledge of the potential alternative disease and MND diagnostic pitfalls are essential, particularly, if the key points are considered, and it is important to rule out treatable causes.

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Conflicts of interest

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