Pitfalls in the diagnosis of motor neurone disease

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Motor neurone disease is characterized by progressive degeneration of upper and lower motor neurones with preservation of cognition. Recognition of classical motor neurone disease is not difficult, but during the early stages both false positive and false negative diagnoses are common. Careful examination, frequent follow-up and ancillary tests are necessary to avoid erroneous diagnoses.

The classification of motor neurone disease (MND) is complicated by the differing use of nomenclature between the USA and Europe. In the USA, 'amyotrophic lateral sclerosis (ALS)' is often used to refer to all forms of MND, encompassing progressive muscular atrophy, primary lateral sclerosis and progressive bulbar palsy. In Europe, the term 'ALS' refers to the 'classical' condition characterized by a combination of upper and lower motor neurone signs with progression, and the term 'motor neurone disease' is used as a generic term to describe all forms of motor neurone degeneration.

DIAGNOSTIC CRITERIA

With the advent of clinical trials for MND, it has become increasingly important to define diagnostic criteria that provide a clinically homogenous study population. It may be argued that the rationale for seeking clinical homogeneity is flawed, as it is likely that the pathogenic mechanisms leading to the clinical presentation of MND are heterogeneous. For example, there is a striking clinical similarity between patients with inherited mutations in the SOD1 gene, and the sporadic disease without SOD1 dysfunction.

Notwithstanding this caveat, in 1990, a consensus conference was held at El Escorial in Spain that defined 'levels of certainty' with respect to the diagnosis of MND (Brooks, 1994). A revision of the El Escorial criteria was undertaken in 1998 at Airlie House, Virginia (Miller et al, 1999). The El Escorial and Airlie House criteria have been criticized on the basis that they are unwieldy and difficult to apply in clinical practice, and that they fail to account for burden of disease. The development of less rigorous criteria suitable for clinical practice has been advocated, with the recognition that 'restricted' forms of MND (such as pure bulbar disease, and progressive muscle atrophy) that do not fulfil the El Escorial criteria for 'definite' or 'probable' ALS, are nonetheless invariably fatal, and exhibit many of the characteristic neuropathological features of classical or 'full blown' ALS (Ince et al, 1998; Ross et al, 1998; Belsh, 2000; Traynor et al, 2000b).

Strict adherence to the El Escorial (or Airlie House) criteria limits the number of false positive misdiagnoses of MND (Traynor et al, 2000a). However, the accuracy of diagnosis is achieved at a cost. Patients who fulfil the criteria for probable or definite ALS have advanced disease in which up to 80% of neurones are lost. This obviously has an impact on the required size of current clinical trials, and on the likelihood of a positive trial outcome.

INITIAL PRESENTATION OF MND: AVOIDING FALSE-NEGATIVE DIAGNOSES

Forty per cent of patients with MND are initially mis-diagnosed (Belsh and Shiffman, 1990). In Ireland and the UK, most patients first present to their general practitioners. Those with bulbar symptoms are often referred to ear, nose and throat surgeons, or to general physicians. The initial referring diagnosis may be that of a cerebrovascular accident, local vocal cord pathology or oesophageal dysfunction. Those with limb onset may be referred to rheumatologists, orthopaedic surgeons or neurosurgeons. Initial diagnoses in this group may include arthritis, entrapment neuropathy, thoracic outlet syndrome, cervical spondylosis or lumbar disc disease (*Table 1*).

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TABLE 1.
Commonest reasons for false negative diagnoses

The attribution of symptoms to a pre-existing disease such as rheumatoid arthritis, cervical spondylosis or osteoporosis
The misinterpretation of results of electrophysiological and neuroimaging data
A lack of familiarity with motor neurone disease and a failure to recognize the neurological nature of the condition

In two recent prospective population-based studies, the average time from first symptom to correct diagnosis was 8–12 months (Traynor et al, 1999; Chio, 2000), although other retrospective studies have reported a delay of 12–17 months from first symptom to diagnosis (Chio, 1999). The delay in diagnosis varies with regard to the site of onset of first symptoms, the presence or absence of fasciculations, and the stage at which a neurologist, as opposed to another specialist, is consulted.

Careful clinical examination and appropriate use of neurophysiological and imaging studies will usually help to establish the correct diagnosis. For example, the presence of tongue fasciculations will point to the involvement of lower motor neurone dysfunction in progressive bulbar palsy, and the presence of a brisk jaw jerk will suggest upper motor neurone dysfunction. Emotional lability suggests bilateral corticobulbar or corticospinal dysfunction. In patients with limb onset, wasting of muscles outside the distribution of commonly entrapped nerves, the preservation of sensation, the presence of fasciculations, and the finding of brisk deep tendon reflexes in a wasted limb in which there are prominent fasciculations are all highly suggestive of a diagnosis of MND. In the lower extremities, the combination of muscle cramping and fasciculations, brisk deep tendon reflexes and upgoing plantar responses with normal sensation suggests the diagnosis. MND should also be considered in the differential diagnosis of patients who have combined upper and lower motor neurone signs, in whom the upper motor neurone signs are rostral to the lower motor neurone signs.

TABLE 2.
Essential diagnostic tests before diagnosis of motor neurone disease

Routine haematology and biochemistry	
Thyroid function tests	
Serum protein electrophoresis and immune protein electrophoresis	
Lumbar puncture	
Analysis for trinucleotide expansion within the androgen receptor gene (in males with lower motor neurone syndrome of bulbar and proximal musculature)	
Neuroimaging	MRI brain (in patients with predominantly upper motor neurone signs)
	MRI spine (in patients with upper motor neurone signs caudal to lower motor neurone signs, and no bulbar features)
Neurophysiology	Extensive nerve conduction studies (in patients with predominantly lower motor neurone signs)
	EMG of 4 limbs and bulbar musculature
Muscle biopsy (if EMG is atypical or unusual myopathy is suspected)	
Hexosaminidase A and B activity (in susceptible Ashkenazi Jewish population)	
Very long chain fatty acids (in patients with positive family history and predominantly upper motor neurone signs)	

EMG = electromyography; MRI = magnetic resonance imaging

DIAGNOSTIC TESTS

There are a number of diagnostic tests which should be undertaken before MND is diagnosed (*Table 2*).

Neurophysiology

There is no definitive diagnostic test for MND. The combination of suggestive clinical signs with negative imaging supports the diagnosis. Progression of the condition is a prerequisite for diagnosis. Neurophysiological studies can assist in the diagnosis by demonstrating ongoing denervation (fibrillation potentials and positive sharp waves) and re-innervation (large polyphasic units) in affected and clinically unaffected limbs, with normal sensation, and normal or near-normal motor nerve conduction velocities. At present, there are no validated, reliable and accessible neurophysiological investigations to establish the presence of upper motor neurone dysfunction, although a number of recent studies using transcortical magnetic stimulation have suggested increased cortical excitability in MND (Eisen, 2000; Pouget et al, 2000).

Neuroimaging

Neuroimaging in MND is usually unremarkable, although magnetic resonance imaging (MRI) may show increased signal on T2 weighted images (Thorpe et al, 1996) and fluid-attenuated inversion recovery (FLAIR) sequences in the internal capsule and along the

corticospinal tracts. However, these changes can also be found in apparently normal controls, and cannot be used as diagnostic markers (Waragai, 1997). The current role of neuroimaging in MND is to rule out other pathological processes that could otherwise account for the clinical symptoms.

MIMIC SYNDROMES AND FALSE POSITIVE DIAGNOSES

Up to 10% of patients initially diagnosed as having MND are ultimately re-diagnosed as having another disease (Davenport et al, 1996; Traynor et al, 2000a). This is because MND is primarily a clinical diagnosis for which there is no definitive diagnostic test, and failure to extensively search for potentially treatable diseases that can superficially resemble MND can lead to error. Two prospective population-based studies have identified the commonest mimic syndromes, and have outlined strategies to limit false positive diagnoses (Davenport et al, 1996; Traynor et al, 2000a). One of the keys to diagnostic revision in both studies was the failure of symptoms or disability to progress as rapidly as expected.

Common mimic syndromes

Multifocal motor neuropathy with conduction block: This condition represented 21% of false positive diagnoses in the recently published Irish study (Traynor et al, 2000a) and 4% of the Scottish study (Davenport et al, 1996). Multifocal motor neuropathy (MMN) is characterized by distal asymmetric-onset weakness, often with prominent cramping, activity-induced fasciculations and a normal sensory exam. Deep tendon reflexes may be preserved, although upper motor neurone signs are absent. MMN is probably an immune-mediated polyneuropathy. The majority of patients with MMN improve following infusion of intravenous gammaglobulin. Refractory patients may respond to cyclophosphamide.

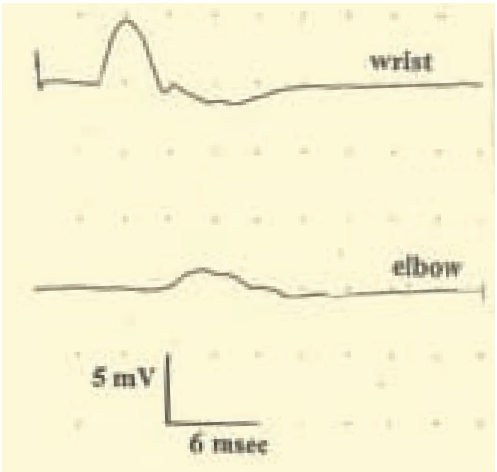

Figure 1. Partial motor conduction block. Compound muscle action potentials recorded from the right abductor pollicis muscle of a 43-year-old man after supramaximal stimulation of the median nerve at the wrist and elbow. The wrist–elbow conduction velocity was 45m/sec. MV = millivolts; msec = milliseconds.

The diagnosis of MMN is established by careful neurophysiological evaluation (*Figure 1*). The condition should be considered in patients presenting with a pure lower motor neurone syndrome with prominent cramping. Weakness may be disproportionate to the degree of wasting, and occasionally selected muscle groups may exhibit hypertrophy. Extensive nerve conduction studies of affected limbs should be performed to look for evidence of conduction block and dispersion. Titres of anti-GM1 and antiGM2 antibodies may be elevated in MMN, although these antibodies can also be elevated in MND, and cannot be used as a definitive diagnostic marker for MMN (Biessels et al, 1997) (*Table 3*).

TABLE 3.
Clinical features that should lead to reconsideration of the diagnosis of motor neurone disease

History of poliomyelitis
Family history with no affected females and no male to male transmission
Symmetrical signs
Pure upper or pure lower motor neurone syndrome
Upper motor signs caudal to lower motor neurone signs, with no bulbar involvement
Failure to progress
Development of sensory signs
Development of sphincter disturbances

Cervical myelopathy: Cervical myelopathy accounts for 3–19% of misdiagnoses (Davenport et al, 1996; Traynor et al, 2000a). Clinical features of myelopathy can mimic ALS closely, although the presence of sensory symptoms and the relatively slow progression of most patients with cervical myelopathy should alert the clinician to the possibility of an alternative diagnosis. In general, patients who present with upper motor neurone signs caudal to lower motor neurone signs, and who have no bulbar signs or symptoms should undergo MRI of the cervical spine.

Kennedy's disease: Kennedy's disease is an X-linked lower motor neurone syndrome that characteristically presents in middle life with bulbar dysfunction, peri-oral fasciculations and proximal muscle weakness. Fifty per cent of those affected have gynaecomastia. The condition is associated with an expansion of trinucleotide repeats in the androgen receptor gene. A family history of affected male relatives may be elicited. The condition should be separated from MND, as it carries a better prognosis, and genetic counselling of affected families should be considered. Diagnosis is established by DNA analysis for trinucleotide repeats.

Post-polio spinal muscle atrophy: A small percentage of patients with a remote history of poliomyelitis develop new onset muscle weakness and wasting in previously strong limbs. Failure to establish a prior history of polio can lead to the erroneous diagnosis of MND. Most patients with post-polio spinal muscle atrophy progress slowly and do not exhibit upper motor neurone signs. Electromyography of affected limbs demonstrates giant polyphasic motor units, signifying long-standing re-innervation. There is no evidence that a prior history of poliomyelitis predisposes to the subsequent development of MND.

Myopathies: ***Inclusion body myositis:*** Inclusion body myositis is a rare myopathy that presents with weakness of quadriceps, wrist extensors and finger extensors. Some patients also complain of dysphagia. Deep tendon reflexes may be preserved, and creatine phosphokinase may be normal. Upper motor neurone signs are absent. The condition is slowly progressive. Electromyography demonstrates combined myopathic and neuropathic features. Failure to recognize the condition or incomplete neurophysiological studies can lead to the erroneous diagnosis of MND. The diagnosis of inclusion body myositis is confirmed by muscle biopsy, which shows characteristic rimmed vacuoles and myeloid inclusions on electron microscopy.

Thyrotoxic myopathy: Thyrotoxic myopathy can present with bulbar dysfunction. The combination of weight loss and dysphagia, and the occasional occurrence of fasciculations can lead to diagnosis of bulbar onset MND. Correct diagnosis can be established by careful electromyography of bulbar-innervated muscle, and by the performance of thyroid function tests. The latter are recommended in the routine evaluation of all patients with suspected MND.

Other upper motor neurone syndromes and rare diseases: Pure motor forms of multiple sclerosis, hereditary spastic paraplegia and adreno-myeloneuropathy can be misdiagnosed as the primary lateral sclerosis form of MND. Differential diagnosis can be difficult in these circumstances, as progression is slow in all of these conditions. Patients presenting with purely upper motor neurone syndromes should undergo extensive investigations including neuroimaging, CSF analysis for oligoclonal banding, serum analysis for very long chain fatty acids, extensive nerve conduction studies and, where appropriate, family members should be examined. In those patients with negative investigations and a slowly evolving upper motor neurone syndrome, repeated clinical examination and regular neurophysiological studies should be performed to seek evidence of lower motor neurone involvement.

Adult-onset Tay–Sachs disease can present as a motor neurone degeneration, and hexosaminidase A and B levels should be measured, particularly in patients of Ashkenazi Jewish extraction.

Variants of MND

'Paraneoplastic' MND: The association between MND and neoplastic disease is controversial. An increased occurrence of neoplastic disease has not been convincingly demonstrated in prospective epidemiological studies (Chio et al, 1988; O Hardiman unpublished observations, 1993–99). There may be a rare association between lymphoproliferative disease and the presence of MND (Gordon et al, 1997), although case controlled studies have not been performed to date to verify this observation. There are anecdotal reports of remission of MND following treatment of the lymphoproliferative disorder. Similarly, although the true incidence and significance of paraproteins in MND remains uncertain, serum protein electrophoresis is recommended in the evaluation of patients with pure lower motor neurone syndromes (Rowland et al, 1982).

Recently, Forsyth et al (1997) described three patients with cancer, antineuronal antibodies and atypical MND, and a further five with primary lateral sclerosis and breast carcinoma. Detailed case controlled studies are required to clarify this possible association.

At present, patients with typical MND do not require an extensive evaluation for neoplastic disease unless there are other clinical findings that independently warrant further investigations.

CONCLUSIONS

MND is a rare condition. In its classical form, it is easily recognizable. However, in its early stages, the condition is misdiagnosed in up to 40% of patients. As there is no definitive test to establish the diagnosis, careful attention to clinical examination with appropriate use of ancillary investigations is required. Ten per cent of patients who are diagnosed as suffering from MND have a 'mimic syndrome'. A mimic syndrome should be considered in patients whose condition fails to progress. Differential diagnosis may require detailed neurophysiology, neuroimaging and specific enzymatic and serologic testing in selected cases. There is no convincing evidence that patients with MND require investigation for occult neoplasia. HM

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KEY POINTS

- Motor neurone disease is a fatal disorder of upper and lower motor neurones with preservation of cognition.
- Forty per cent of patients are initially diagnosed as suffering from another condition. The risk of misdiagnosis is higher in those patients that have not been reviewed by a neurologist.
- Diagnosis is by exclusion and is based on clinical examination with the appropriate use of laboratory tests to rule out other conditions.
- Ten per cent of patients diagnosed as suffering from motor neurone disease have another condition. Failure of clinical signs to progress should alert the clinician to the possibility of another diagnosis.
- Patients with combined upper and lower motor neurone signs, in whom the upper motor neurone signs are caudal to the lower motor neurone signs, and in whom there are no bulbar features should routinely undergo neuroradiological imaging of the cervical spine.
- Patients with only lower motor neurone signs should undergo extensive nerve conduction studies to look for evidence of conduction block.