CME Article

Motor neurone disease: clinical features, diagnosis, diagnostic pitfalls and prognostic markers

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ABSTRACT

Motor neurone disease (MND) is a rapidly progressive adult-onset neurodegenerative disorder. In recent years, there has been an increased understanding regarding the epidemiology and clinical features of the different variants of MND. In addition, new diagnostic criteria have been proposed to increase the sensitivity of the diagnosis. This review highlights these new concepts and discusses the differential diagnoses of MND, highlighting the common pitfalls and misdiagnoses. It also discusses the prognostic markers for MND and a possible change in the natural history of the disease course.

Keywords: motor neurone disease

Singapore Med J 2010;51(5):367-373

INTRODUCTION

Motor neurone disease (MND), interchangeably known as amyotrophic lateral sclerosis (ALS) in many countries, was originally described by the French physician Jean-Martin Charcot.[1]

EPIDEMIOLOGY

MND is one of the most common adult-onset neurodegenerative diseases. There is increasing evidence of ethnic variation in the incidence of MND.[2] Within the Caucasian population of Europe and North America, where most of the studies have been conducted, the lowest reported incidence of MND was 0.6 per 100,000 person-years in Italy,[3,4] and the highest reported was 2.4 per 100,000 person-years in Finland.[5] In two studies conducted within the Asian population, the one from China showed an incidence of 0.3 per 100,000 person-years,[6] while another from Japan showed an incidence of 0.7 per 100,000 person-years.[7] In the only well-conducted study of MND incidence in black African populations, the incidence of MND was noted to be 0.9 per 100,000 person-years in Libya.[8] Studies of Central and South American populations have reported the incidence of MND to range from 0.3[9] to 1.7[10] per 100,000 person-years, although it is difficult to assign a single rate under the term Hispanic due to the diversity of heritage of these populations. In addition, three population-wide MND mortality studies in the United States have shown a lower mortality rate among African Americans and Hispanic populations when compared to the white population.[11-13] Therefore, epidemiological studies suggest that the incidence of MND is highest in the Caucasian population.

The incidence of MND is said to be increasing, but this is probably the result of improved diagnosis, better awareness of the disease and an aging population.[14] The incidence increases after the age of 40 years, peaks in the late 60s and early 70s, and declines rapidly after that.[15] Death occurs in most patients within two to five years after diagnosis.[16] Recent studies have suggested that the male to female ratio in MND is tending toward one.[15] 5%–10% of the cases are familial, and the rest are sporadic.

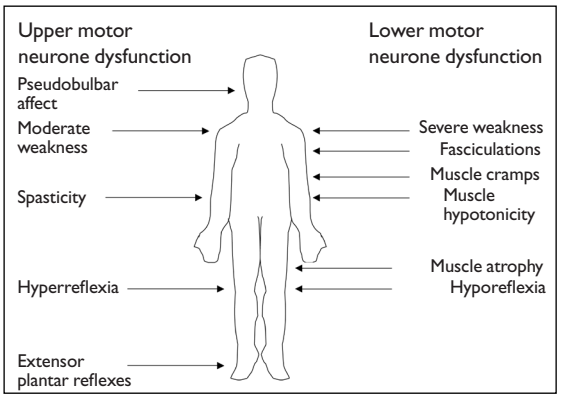

Fig. 1 Signs and symptoms of upper and lower motor neurone dysfunction in motor neurone disease.

CLINICAL FEATURES

The clinical spectrum in MND results from a degeneration of upper motor neurones in the motor cortex, lower motor neurones of the brainstem and spinal cord, or both (Fig. 1). At presentation, the most common variant is amyotrophic lateral sclerosis (ALS) (in this context, the term 'ALS' or 'ALS variant' refers to a specific form of MND), which gives rise to a combination of upper and lower motor neurone signs and symptoms. In one study, 94% of patients

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Table I. Revised El Escorial criteria for the diagnosis of ALS.[38,39]

Definite ALS	Upper and lower motor neurone signs in at least three body regions (upper limb, lower limb, bulbar, thoracic).
Clinically probable ALS	Upper and lower motor neurone signs in at least two regions, with some upper motor neurone signs necessarily rostral to the lower motor neurone signs.
Clinically probable ALS: laboratory-supported ALS	Clinical signs of upper and lower motor neurone dysfunction in only one region, or when upper motor neurone signs alone are present in one region and lower motor neurone signs defined by electromyographic criteria are present in at least two limbs, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
Clinically possible ALS	Clinical signs of upper and lower motor neurone dysfunction are found together in only one region, or upper motor neurone signs are found alone in two or more regions, or lower motor neurone signs are found rostral to upper motor neurone signs and the diagnosis of clinically probable: laboratory-supported ALS cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiological, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded.

ALS: amyotrophic lateral sclerosis

had the ALS variant of MND.[17] The manifestation of upper and lower motor neurone features usually begins focally, and progresses to involve contiguous regions of the body with decreasing severity.[18] Approximately two-thirds of cases start in the limbs and one-third, in the bulbar group of muscles; only a very small percentage of them begin with respiratory muscle involvement.[17,18]

There are two other main variants of MND: primary lateral sclerosis (PLS) and progressive muscular atrophy (PMA). One study showed that PLS accounts for around 2% of MND cases, and PMA for 4% of cases.[17] Many of these patients tend to progress to the ALS variant over time.[19-21] Progressive bulbar palsy is a term that is often used to describe the bulbar onset of MND, and is not strictly a variant in its own right.

PLS is a pure upper motor neurone syndrome that exhibits progressive upper motor neurone degeneration with limb and bulbar dysfunction, with no lower motor neurone features. There is still a debate as to whether PLS is a separate entity from the ALS variant or simply a different manifestation of MND. Compared to patients with an ALS variant, patients with PLS tend to present five to ten years earlier, have less limb wasting and bulbar symptoms during the course of the disease, and survive six to seven years longer.[19,20]

PMA is associated with a degeneration of the lower motor neurones of the spinal cord in the absence of upper motor neurone and bulbar features. Once again, there is controversy with regard to the validity of PMA as a distinct entity from the ALS variant of MND. Some have reported a slowly progressive course for PMA, one that can be as long as 20 to 30 years, but this is not always the case.[21-23]

The classical concept that MND only affects the motor system is obsolete. MND is now considered to be a multisystem neurodegenerative disease. There is increasing clinical evidence for autonomic dysfunction[24,25] sensory abnormalities[25-28] and ophthalmoplegia[25,29] in MND. In addition, there are good pathological accounts of the involvement of sympathetic and parasympathetic neurones,[25,30-32] Onuf's nucleus (which innervates the pelvic floor sphincteric muscles),[25,32,33] peripheral sensory nerves[25-27] and oculomotor nuclei.[25,29] However, it must be emphasised that in the majority of patients, the motor dysfunction proves lethal before the development of overt clinical features of the other affected regions of the nervous system. Therefore, in practical terms, the presence of prominent ophthalmoplegia, sensory signs or sphincter dysfunction should raise doubts regarding the diagnosis of MND, unless there is a clear alternative explanation. Death usually results from ventilatory muscle weakness, causing respiratory failure.

Cognitive impairment is increasingly being recognised in MND. Subtle subclinical cognitive defects and frontal lobe dysfunction may be demonstrated in up to half of MND patients with detailed neuropsychological testing.[34,35] Several genetic mutations of MND have been identified in association with frontotemporal dementia and/or parkinsonism.[36] Recently, the TAR DNA-binding protein 43 (TDP-43) was recognised as a major constituent of the neuronal inclusions seen in both MND and frontotemporal dementia,[37] although the function of TDP-43 is still unknown.

DIAGNOSTIC CRITERIA

The revised El Escorial World Federation of Neurology criteria have been used to establish the diagnosis of MND (Table I).[38,39] Essentially, the criteria classify patients into three categories of certainty: 'definite', 'probable' and 'possible', by taking into account their clinical, electrophysiological, neuroimaging, laboratory and neuropathological information. Although the above criteria were developed to promote uniform populations

Table II. Awaji-shima consensus recommendations for diagnostic categories of ALS.[42]

Clinically definite ALS	Clinical or electrophysiological evidence of lower and upper motor neurone signs in the bulbar region and at least two spinal regions, or the presence of lower and upper motor neurone signs in three spinal regions.
Clinically probable ALS	Clinical or electrophysiological evidence of lower or upper motor neurone signs in at least two regions with some upper motor neurone signs necessarily rostral to (above) the lower motor neurone signs.
Clinically possible ALS	Clinical or electrophysiological signs of upper and lower motor neurone dysfunction are found in only one region; or upper motor neurone signs are found alone in two or more regions; or lower motor neurone signs are found rostral to upper motor neurone signs. Neuroimaging and clinical laboratory studies must have been performed and other diagnoses must have been excluded.

ALS: amyotrophic lateral sclerosis

in clinical trials, it has helped to formalise an approach to identify MND reliably by taking into account the clinical and investigational information. The criteria are susceptible to the vagaries of clinical practice, and are not a substitute for clinical experience. About 10% of patients with MND die without becoming eligible for clinical trials because they do not fully meet the revised El Escorial criteria for 'definite' or 'probable' MND.[40]

One of the major criticisms of the revised El Escorial criteria is that they favour clinical signs over electrodiagnostic findings, thereby reducing their sensitivity.[40,41] Therefore, a group of clinical neurophysiologists have recently drawn up recommendations to modify the revised El Escorial criteria, in particular, that electrophysiological evidence of lower motor neurone dysfunction should be equivalent to clinical signs.[42] As a result, it would make redundant the category of *clinically probable ALS: laboratory-supported ALS* in the revised El Escorial criteria. These Awaji-shima consensus recommendations (Table II) are likely to increase the sensitivity of the diagnostic criteria for MND without altering the specificity.[43]

DIFFERENTIAL DIAGNOSES AND DIAGNOSTIC PITFALLS

Although with time, and in the hands of a good diagnostician, the clinical diagnosis of MND is likely to be correct in more than 95% of cases,[44] the diagnosis can be more difficult in the early stages of the disease.[45] The differential diagnosis of MND is wide (Table III). It is important to exclude treatable conditions, of which multifocal motor neuropathy and cervical spondylotic myelopathy are probably the most easily missed.[46] Several of the most common mimics of MND are now discussed in greater detail below.

Multifocal motor neuropathy (MMN) is an immune-mediated demyelinating motor neuropathy that can present very similarly to MND, but is responsive to intravenous immunoglobulin.[47] Clinical features that suggest MMN include the preservation of muscle bulk in weakened muscles and differential weakness across a common terminal motor nerve.[48] Although it is a lower motor neurone syndrome, deep tendon reflexes can be normal or brisk in 20%–30% of MMN cases.[49] Persistent multifocal motor conduction blocks outside common entrapment sites on neurophysiology point toward this diagnosis. Antibodies to the GM1 ganglioside are present in only a small proportion of patients.[48]

Although severe cervical spondylotic myelopathy may sometimes cause confusion with MND, especially if there is spasticity and hyperreflexia in the lower limbs in conjunction with muscle atrophy and fasciculations in the upper limbs, it is unlikely to cause widespread fasciculations, weakness and wasting in the hand muscles.[44] Certainly, the presence of fasciculations in the tongue or legs would be against the diagnosis of cervical myelopathy. Magnetic resonance (MR) imaging is helpful in ruling out spinal cord compression. Nevertheless, approximately 5% of patients with MND have had cervical or lumbar laminectomies early in the course of their disease.[44,50]

Kennedy's disease, or spinobulbar muscular atrophy, is an X-linked trinucleotide repeat disorder with expansion of polyglutamine repeats in the androgen receptor gene.[51] It is a lower motor neurone syndrome with more proximal rather than distal limb weakness, and bulbar muscle weakness. It is characteristically associated with perioral fasciculations, tremor, gynaecomastia and diabetes mellitus, features that are not typically seen in MND.[52-54]

It is not uncommon for patients with inclusion body myositis (IBM) to be misdiagnosed with MND.[55] The pattern of weakness of IBM is characteristic – weakness of deep finger flexors and wrist flexors disproportionate to that of their extensor counterparts, and prominent weakness of the quadriceps. Mild dysphagia may also occur.[56] IBM is associated with an inflammatory infiltrate that also affects non-necrotic muscle fibres,

Table III. Mimics of MND that require consideration and screening investigation(s) for each.

Condition	Investigation(s)
Benign fasciculation and cramp syndrome	Electromyography
Brainstem lesions, e.g. syrinx, stroke	MR imaging
Cervical/lumbar spondylotic myelopathy	MR imaging
Chronic inflammatory demyelinating polyneuropathy	Nerve conduction studies, high protein in cerebrospinal fluid
Heavy metal exposure, e.g. lead	Toxicology screen
Hexosaminidase A and B deficiency	White cell enzymes
Kennedy's disease (X-linked spinobulbar muscular atrophy)	Androgen receptor gene mutation
Lymphoma	Full blood count, imaging of thorax, abdomen and pelvis, diagnostic biopsy
Monoclonal gammopathy	Erythrocyte sedimentation rate, serum protein electrophoresis
Multifocal motor neuropathy	Nerve conduction studies, anti-GM1 ganglioside antibody
Multiple sclerosis	MR imaging, oligoclonal bands in cerebrospinal fluid
Myasthenia gravis	Single-fibre electromyography, anti-acetylcholine receptor antibody
Neurosyphilis	Syphilis serology
Paraneoplastic encephalomyelitis	Anti-neuronal antibodies, screen for underlying malignancy
Polymyositis or inclusion body myositis	Serum creatine kinase, electromyography, muscle biopsy
Post-poliomyelitis	Nerve conduction studies and electromyography
Thyrotoxicosis	Thyroid function tests
Vitamin B_{12} and folate deficiency	Serum vitamin B_{12} and folate levels

MND: motor neurone disease; MR: magnetic resonance

rimmed vacuoles and congophilic inclusions.[56,57] Electromyography reveals both neurogenic and myopathic features. A muscle biopsy is usually required to clinch the diagnosis.

Benign fasciculation and cramp syndrome can be distinguished from MND by the presence of widespread fasciculations without any weakness, wasting or change in deep tendon reflexes. Electromyography may show spontaneous activity, but motor unit morphology is normal.

DIAGNOSTIC PROCESS

There is no specific test for MND. Investigations are carried out to exclude other conditions (Table III). A degree of clinical acumen and common sense is required when deciding which investigations should be carried out in suspected cases. Blood tests should include full blood count, erythrocyte sedimentation rate, a biochemistry screen, serum protein electrophoresis, anti-ganglioside antibodies, thyroid function tests, syphilis serology, serum creatine kinase, vitamin B_{12} and folate levels. A chest radiography should be done, especially in smokers. MR imaging should be carried out to exclude compressive myelopathy and brainstem lesions. Cerebrospinal fluid examination is not required routinely, unless the presentation is atypical. Specialised tests, such as white cell enzymes, should only be used in appropriate circumstances or atypical cases, and they are probably done best in conjunction with advice from a neurologist.

Electrophysiological evaluation is useful for the diagnosis of MND.[58] Repeated investigations may be required as the initial findings at presentation may not fulfill the revised El Escorial criteria[38,39] or Awaji-shima recommendations,[42] and the diagnosis can only be confirmed with disease progression over time. Sensory nerve conduction is normal. Motor conduction velocity in the limbs is usually normal because the primary abnormality is axonal loss, rather than demyelination. It is critical that motor nerve conduction is also assessed in more proximal nerve segments to exclude conduction block. Electromyography is important in establishing the presence of widespread anterior horn cell damage that is unexplained by a single nerve, root or plexus lesion. This involves demonstrating evidence of acute denervation and reinnervation by examining at least two muscles in an affected limb, at least one muscle in a clinically unaffected limb and at least one muscle innervated by a cranial nerve, e.g. sternocleidomastoid or tongue. The assessment of thoracic paraspinal muscles by electromyography provides a useful strategy for differentiating MND from spondylosis because the thoracic paraspinal muscles are frequently affected in MND and spared in spondylotic amyotrophy.[59]

PROGNOSTIC MARKERS

Several poor prognostic factors for survival in MND

have been identified at disease presentation: greater age, a short interval between symptom onset and diagnosis, marked weight loss, markedly reduced forced vital capacity, marked muscle weakness and bulbar onset of the disease.[60] There is a suggestion that MND may be becoming less aggressive over time, with two groups reporting a slightly prolonged survival and slower disease progression in contemporary, compared with historical, patients.[61,62] In one study, this change was independent of potentially disease outcome-modifying therapies such as riluzole (the only drug currently approved for the treatment of MND), non-invasive ventilation and percutaneous gastrostomy.[61]

CONCLUSION

Our knowledge of MND has evolved over the last few years. A better understanding of the epidemiology and clinical features of this disease will enable it to be diagnosed more readily. An awareness of the differential diagnoses and pitfalls of diagnosis is invaluable. Finally, prognostic markers are important in enabling physicians to predict the course of the disease.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME
Multiple Choice Questions (Code SMJ 201005B)

	True	False
Question 1. Regarding the epidemiology of motor neurone disease:		
(a) The incidence is highest in the Asian population.	☐	☐
(b) The incidence is increasing.	☐	☐
(c) Less than 1% of cases are familial.	☐	☐
(d) The incidence peaks after the age of 80 years.	☐	☐
Question 2. Regarding the clinical features of motor neurone disease:		
(a) The majority of cases start with symptoms in the bulbar group of muscles.	☐	☐
(b) The primary lateral sclerosis variant of motor neurone disease is a pure upper motor neurone syndrome.	☐	☐
(c) Subtle cognitive defects and frontal lobe dysfunction can be detected in half of the patients with motor neurone disease.	☐	☐
(d) Motor neurone disease does not affect the oculomotor nuclei or peripheral sensory nerves.	☐	☐
Question 3. The following interventions or treatments have been shown to prolong life in motor neurone disease:		
(a) Intravenous immunoglobulin.	☐	☐
(b) Riluzole.	☐	☐
(c) Donezepil.	☐	☐
(d) Percutaneous gastrostomy.	☐	☐
Question 4. The following differential diagnoses of motor neurone disease are paired with the most appropriate diagnostic test:		
(a) Kennedy's disease – androgen gene receptor mutation.	☐	☐
(b) Myasthenia gravis – nerve conduction studies.	☐	☐
(c) Paraneoplastic encephalomyelitis – muscle biopsy.	☐	☐
(d) Benign fasciculation and cramp syndrome – electromyography.	☐	☐
Question 5. Indicate whether the following statements are true or false:		
(a) Motor conduction velocity in the limbs on nerve conduction studies in motor neurone disease is usually normal.	☐	☐
(b) Motor conduction blocks in the proximal nerve segments in the limbs on nerve conduction studies are common in motor neurone disease.	☐	☐
(c) Sensory nerve conduction on nerve conduction studies is usually normal in motor neurone disease.	☐	☐
(d) Assessment of lumbar paraspinal muscles by electromyography is useful in differentiating motor neurone disease from spondylotic amyotrophy.	☐	☐

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SUBMISSION INSTRUCTIONS:
(1) Log on at the SMJ website: http://www.sma.org.sg/cme/smj and select the appropriate set of questions. (2) Select your answers and provide your name, email address and MCR number. Click on "Submit answers" to submit.

RESULTS:
(1) Answers will be published in the SMJ July 2010 issue. (2) The MCR numbers of successful candidates will be posted online at www.sma.org.sg/cme/smj by 2 August 2010. (3) All online submissions will receive an automatic email acknowledgment. (4) Passing mark is 60%. No mark will be deducted for incorrect answers. (5) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.

Deadline for submission: (May 2010 SMJ 3B CME programme): 12 noon, 26 July 2010.