Motor neuron disease is a devastating condition characterised by degeneration of motor nerves. Many of the presenting symptoms, such as fatigue, muscle weakness and difficulty in swallowing have a broad differential diagnoses in the elderly population. Dr Sheba Azam and Professor PN Leigh explain how ensuring quality of life for patients requires preventing unnecessary delay in diagnosis and early referral to an appropriate multidisciplinary team.

Amyotrophic lateral sclerosis (ALS) also known as motor neuron disease (MND) (the terms are used interchangeably), was first described in 1869 by the French neurologist Jean-Martin Charcot. It is a progressive, fatal neurological disease characterised by degeneration of motor nerve cells in the motor cortex, corticospinal tract and the spinal cord anterior horn cells. The degeneration of motor nerve cells results in progressive muscle wasting leading to significant disability and ultimately death. Death usually results from respiratory failure due to weakness of the respiratory muscles.

Incidence and prevalence
The worldwide incidence of MND is approximately two per 100,000 and the prevalence is four to seven per 100,000. There are 1,200 new cases of MND per year in the UK and the estimated number of people with MND is up to 5,000. Approximately 80 per cent of MND cases begin between the ages of 40–70, with the average age of onset being age 55. Cases have been found in persons as young as 12 and as old as 98. Before the age of 60, men get MND more than women (1.5 to 1.0 ratio). After the age of 60 the ratio of men to women is nearly one to one.

Diagnosis may be particularly difficult with the very old due to incidental conditions (eg, cervical spondolytic myelopathy and radiculopathy) and cognitive changes. Thus, misdiagnosis as well as under-investigation has been suggested as possible causes of an apparent decrease in the incidence of MND in later life.

Prognostic factors
Although the average survival in MND is around 36 months, some patients live for 10 years or more. Certain phenotypic variants appear to determine survival rates. Using information held in a tertiary referral MND database, a group of researchers analysed data on onset of disease, site of onset and duration of survival. The authors concluded that typical MND with bulbar onset, onset later in life or in the definite category of El Escorial (where the World Federation of Neurologist meet to decide diagnostic criteria) at presentation, did not rule out a long survival, although younger onset and pure upper motor neuron signs at presentation were more likely to be associated with a better prognosis.

Pathogenic mechanisms
The precise pathogenic mechanisms underlying the disease process in MND are unknown. A major advance in understanding motor neuron degeneration was made in 1993 in familial cases of the disease. Five to 10 per cent of cases of MND are familial. Twenty per cent of these familial cases are caused by a mutation in the superoxide dismutase 1 gene.
dismutase 1 (SOD1), an antioxidant defence protein. A body of evidence suggests that the mutant protein exerts a cell-specific toxic gain of function that may be related to abnormal protein folding and aggregate formation. In sporadic cases of MND it is likely that multiple pathogenic mechanisms contribute to the death of motor nerve cells particularly vulnerable to these processes. A combination of genetic susceptibility and environmental factors are likely to interact in order to trigger the degenerative process via a number of pathogenic mechanisms including:

- oxidative stress;
- excitotoxicity (the pathological process in which neurons are damaged because of excessive and prolonged activation of excitatory receptors);
- neurofilament dysfunction (abnormal accumulation of neurofilament causing dysfunction of axonal transport);
- protein aggregation;
- mitochondrial dysfunction;
- inflammation; and
- apoptosis.

### Diagnosis

The average delay from symptom onset to diagnosis of MND is about 14 months and may be even longer in the elderly population where, at the onset of MND, the symptoms may be so slight they are frequently overlooked or falsely attributed to ‘old age’ or other pre-existing neurological conditions common in this age group (eg, cervical spondylosis, stroke). The diagnosis of MND remains a clinical one, dependent on history-taking and examination skills.

A careful history and neurological examination must search for clinical evidence of upper motor neuron (UMN) and lower motor neuron (LMN) signs in four regions (brainstem, cervical, thoracic and lumbosacral). Symptoms of MND include fatigue, progressive muscle weakness in limb and bulbar (speech or swallowing) regions, and muscle cramps. In more advanced stages patients may develop respiratory muscle weakness and complain of early morning headaches, daytime fatigue and sleepiness, poor concentration, disturbed sleep, anorexia, dyspnoea and orthopnoea. In rare cases patients with MND may present with type 2 respiratory failure. Patients may also develop difficulty controlling emotion and may sometimes laugh or cry inappropriately. This pseudobulbar affect is thought to be caused by the loss of frontal inhibition over the bulbar nuclei involved in these emotions.

There is now much clinical and pathological evidence that MND is associated with dementia. MND with dementia is a frontotemporal dementia with a characteristic molecular pathology. Frontotemporal dementia is rare (five per cent of MND patients), although as much as 20–40 per cent of patients with MND show cognitive impairments of frontal type. These impairments may be more common in patients with the pseudobulbar syndrome.

Diagnostic criteria were agreed upon by an international group of clinicians, under the leadership of the World Federation of Neurology Committee on Motor Neuron Diseases in 1994 and subsequently revised in 2000. The El Escorial criteria for the diagnosis of ALS (MND) were initially developed for use in clinical trials and became a gold standard as an entry criterion for clinical research. Electrophysiology is used to provide supporting evidence for the diagnosis of MND and also for excluding other possible differential diagnoses.

There are a number of ALS-like syndromes that must be recognised. These include pure lower as well as pure upper motor neuron syndromes that occur as a result of other non-ALS (MND) pathogenic processes and do not represent other forms of ALS (MND). These include multifocal motor neuropathy, post-polio motor neuropathy, paraneoplastic syndromes, hyperthyroidism and hyperparathyroidism. Although cervical spondylosis is likely to present with sensory symptoms it is an important diagnosis to exclude in the elderly population.

### Management of MND, a multidisciplinary approach

There is currently only one drug licensed for the treatment of MND. Riluzole is believed to reduce damage to motor neurons by decreasing the presynaptic release of glutamate and by directly blocking its action at the NMDA receptor (glutamate receptor/N-methyl d-aspartate receptor). There is strong evidence that riluzole treatment at 100mg daily is associated with a small increase in survival of between two to four months at 18 months. Under the National Institute for Health and Clinical Excellence guidelines riluzole
therapy should be initiated by a neurologist with MND expertise, with routine supervision through locally agreed shared care protocols\(^\text{13}\). A side effect of riluzole (in less than five per cent of patients) is abnormal hepatic enzyme function and blood should be checked monthly for the first three months, then every three months for a further nine months, then six to 12 monthly. Symptomatic side effects in less than 10 per cent include nausea, anorexia, fatigue, stiffness, diarrhoea and constipation.

Other treatments for MND are designed to relieve symptoms and improve the quality of life for patients. This supportive care is best provided by multidisciplinary teams of healthcare professionals such as:

- physicians (GPs);
- pharmacists;
- specialist nurse;
- physiotherapist;
- occupational, speech and language therapists;
- dietician;
- social workers; and
- a local palliative care team.

Physicians can prescribe medications to help reduce fatigue, ease muscle cramps, control spasticity, and reduce excess saliva and phlegm. Other common symptoms in MND that require treatment are pain, depression, sleep disturbances and constipation.

The measure of respiratory muscle weakness most often used in clinical practice is the vital capacity (VC) either slow or forced. VC has limitations as a measure of respiratory muscle function in MND. Patients with bulbar onset MND cannot perform the test accurately. VC is also relatively insensitive to significant changes in respiratory function\(^\text{14}\). Sniff nasal pressure (SNP) is a simple and reliable measure of respiratory muscle weakness\(^\text{14}\). At a meeting of the European ALS/MND consortium, provisional criteria for initiating non-invasive ventilation was agreed\(^\text{15}\).

Non-invasive intermittent positive pressure ventilation via a nasal or face mask is an efficient means of alleviating symptoms of chronic respiratory insufficiency. It improves quality of sleep and cognitive function and relieves morning headaches\(^\text{16}\).

Patients and caregivers can learn from speech and language therapists and dieticians how to plan and prepare numerous small meals throughout the day that provide enough calories, fibre and fluid —
Key points

- Motor neuron disease (MND) is a fatal neurological condition characterised by degeneration of motor nerve cells.
- Diagnosis may be particularly difficult in the elderly due to coexisting pathology (eg, cervical myelopathy/radiculopathy) and cognitive changes.
- A delay in diagnosis means a delay in initiating care.
- Early referral to a multidisciplinary team is important for reducing patient and carer burden.

and how to avoid foods that are difficult to swallow. Patients may begin using suction devices to remove excess fluids or saliva and prevent choking. Supervision by the speech and language therapist, dietician and physician throughout the course of the disease is important and contributes to decisions on gastrostomy tube feeding.

Percutaneous endoscopic gastrostomy (PEG) is the standardised procedure for MND patients offering maintenance of good nutrition and prolonged survival. Radiologically inserted gastrostomy (RIG) offers several advantages over PEG. The procedure for RIG requires only a local anaesthetic as opposed to the sedation required for a PEG. RIG does not require the patient to swallow an endoscopic tube and can potentially be carried out with the patient remaining upright. Finally the procedure for RIG is generally tolerated well in patients with a VC of <50 per cent. For a summary of assessment for PEG/RIG procedures at the King’s MND Care and Research Centre see reference 38.

Conclusion

The diagnosis of MND is a devastating one for patients and relatives. A delay in diagnosis inevitably means a delay in initiating care, adding to patient and relative burden. Once a patient has been told the diagnosis it is important to liaise closely with the family GP, who should be involved from the start. This is particularly invaluable for expediting referrals to community services and local palliative care teams who work in consultation with physicians to ensure proper medication, pain control and other care affecting the quality of life of patients. The palliative care team can also counsel patients and caregivers about end-of-life issues. In summary, a coordinated team approach is essential for the care and support of MND patients and their relatives.

Conflict of interest: none declared.

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