MOTOR NEURONE DISEASE: (1) CLINICAL FEATURES AND PATHOGENESIS

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This is the first of two articles on motor neurone disease. It describes the main clinical features and diagnostic criteria and outlines the current understanding of its pathogenesis. The second article will look at the management of the disease.

AFTER Parkinson’s disease and Alzheimer’s disease, motor neurone disease is the third most common adult-onset neurodegenerative disorder. The condition has an incidence of about one to two per 100,000,1 and a prevalence in the United Kingdom population of four to six per 100,000.2

Despite the many recent advances made in developing understanding of the pathogenesis of the disease, specialists and non-specialists alike still find many aspects of motor neurone disease difficult to address. In particular, many are pessimistic about the treatment they are able to offer patients, their confidence in being able to manage patient symptoms and their ability to convey hope, especially in view of the generally poor prognosis the illness carries. This attitude is further exaggerated by the current limited availability of disease modifying treatments.

However, with the help of a multidisciplinary team, an individualised treatment regimen can be devised to ensure that all aspects of symptomatic relief are addressed and essential psychosocial support can be given to both patients and carers. Care in this context can bring about significant improvement in patient wellbeing.

CLINICAL FEATURES

The clinical features of motor neurone disease are due to a progressive degeneration of lower motor neurones in the spinal cord and brainstem and of upper motor neurones in the motor cortex. This leads to denervation atrophy of skeletal muscles, paralysis and ultimately death. Depending on the regions affected by the disease process, the presenting symptoms vary from patient to patient. Generally three main patterns of onset occur, involving the limb, bulbar (speech and swallowing) and respiratory musculature.

Limb onset Limb onset is the most common pattern and is seen in about 60 to 75 per cent of cases. Early symptoms are often asymmetrical and may initially involve only one limb. When disease onset is in the lower limbs, initially some patients may notice nothing more specifically wrong than feeling slightly more fatigued during a regular walk. Other patients may have noticed a slight difficulty with walking, having a tendency to stumble, especially on uneven ground. “Heaviness” and “stiffness” of the legs are commonly reported symptoms.

Further difficulties include problems when negotiating flights of stairs or rising from chairs. Clinically, wasting of the muscles is often seen in the tibialis anterior. Fasciculation (twitching caused by contraction of muscle motor units) is commonly observed in the bulky proximal lower limb muscles. Weakness is demonstrated earliest in hip flexors and ankle dorsiflexors, a common early sign being foot-drop. However, the quadriceps and muscles involved in ankle...
plantar flexion are often relatively spared. In the upper limbs it may be first noticed that the intricate hand movements involved in dealing with zip fastenings, buttons and shoelaces become increasingly difficult. The gripping and turning movements required for using keys and opening bottles, for example, may also become a problem, as can movements involved in lifting the arms above the head, such as when combing or washing the hair.

A characteristic pattern of weakness in the upper limbs is seen with early involvement of the small muscles of the hand. The muscles which flex the fingers and which straighten the elbow are often relatively spared. It is common to see wasting of the small muscles of the hands. Fasciculation (twisting) is often observed, particularly in the proximal muscles.

**Bulbar onset** Bulbar onset occurs in about 20 per cent of cases. Initially symptoms may include slurring of the speech, the voice then becoming affected in several ways. If spasticity of the bulbar musculature occurs, the voice takes on a tight, “strangled” quality. Hoarseness can result from paresis of the vocal cords, and any weakness of the palatal muscles will give a nasal sound to the voice. Usually when speech problems become severe the patient also has swallowing difficulties. Initially this may only involve liquids; patients describe nasal regurgitation of fluids if nasopharyngeal incompetence is present.

Further difficulties with bulbar function, such as the manipulation of food within the mouth and difficulty with co-ordinating swallowing movements can occur. At this stage, distressing choking and coughing spells may be a feature, especially if thoracic respiratory musculature involvement is also present, making effective coughing and clearing of the throat difficult. When the degree of dysphagia is moderate to severe, drooling of saliva can become a troublesome symptom. Clinically a combination of wasting, fasciculation, spasticity and weakness of the tongue may be evident along with poor elevation of the soft palate and an exaggerated jaw jerk.

**Respiratory onset** Respiratory onset is the least common pattern of presentation. Respiratory failure occurs as a result of the loss of bulbar, cervical and thoracic motor neurones. Inspiratory muscles are preferentially affected. A decrease in lung vital capacity to 50 per cent of that predicted is often associated with respiratory symptoms. Initially patients may complain of mild dyspnoea on exertion or on lying flat. Dyspnoea gradually worsens as the disease progresses, becoming present at rest.

Symptoms of subtle respiratory involvement, such as those described in sleep apnoea, should be sought because patients will often not volunteer this information unless specifically questioned. Features may include snoring, apnoeas and frequent waking during sleep. Early morning headaches, feeling unrefreshed on waking and sleepiness during the day are also features. Anorexia, sweats and tremors may also indicate significant respiratory muscle involvement in motor neurone disease.

As well as limb, respiratory and bulbar muscular weakness, involvement of neck and trunk musculature is often seen as the disease progresses, showing particular involvement of those muscles involved in neck extension. This can lead to the patient experiencing problems in trying to maintain a stable upright posture of the trunk and head. Intellect is usually well preserved although detailed neuropsychological testing has shown that subclinical changes, particularly affecting the frontal function, are more common than previously recognised. Dementia, however, is seen in only approximately 3 to 5 per cent of cases. Clinical and pathological studies do show that there is involvement of extramotor parts of the central nervous system. These include changes in other long tracts, including sensory and spinocerebellar pathways. Although overt sensory loss is not usually seen, some patients do occasionally describe some alteration in sensory perception.

Involvement of Onuf’s nucleus — the motor nucleus in the sacral portion of the spinal cord responsible for the control of sphincter function — is usually not seen. In addition, the third, fourth and sixth cranial nerves responsible for eye movements also seem to be relatively resistant to the degenerative process in motor neurone disease, although there are case reports in the literature detailing patients who have been maintained on long-term invasive ventilatory support eventually developing eye movement disorders.

### Diagnosis

As yet, no disease-specific test for motor neurone disease exists and the diagnosis is based on clinical findings. Diagnostic difficulties can arise because the disease represents a heterogeneous group of disorders. The different subgroups vary in their presentations and clinical courses.

To address this problem, a research group on neuromuscular disorders from the World Federation of Neurology laid down criteria for the diagnosis of motor neurone disease in 1994 (El Escorial criteria). Essentially the diagnosis can be made if evidence of mixed upper motor neurone (UMN) and lower motor neurone (LMN) damage, in the absence of sensory abnormalities, is shown on clinical examination. These signs must show progressive spread within a region or to other regions over a period of time and be present in the absence of electrophysiological and neuroimaging techniques, suggesting disease processes which might otherwise explain the clinical picture. This diagnosis can then be further stratified into the categories of definite, probable, possible and suspected motor neurone disease.

Clinically, there are four main recognised subgroups of motor neurone disease. These are amyotrophic lateral sclerosis (clinically showing a mixture of UMN and LMN signs), progressive bulbar palsy (with the bulbar musculature showing possibly both UMN and LMN signs), progressive muscular atrophy (showing purely LMN signs) and primary lateral sclerosis (showing purely UMN signs).

UMN signs on examination include increased limb tone, muscular weakness, brisk tendon reflexes and extensor plantar responses. LMN signs include muscle wasting, fasciculation and weakness with reduced or absent tendon reflexes. Despite this stratified classification, however, in about 10 per cent of cases, it still might not be possible to be confident about the diagnosis until several months have elapsed.

The most important investigation to confirm the diagnosis of motor neurone disease is neurophysiological assessment with electromyography and nerve conduction studies. Imaging of the brain and spinal cord may be necessary to exclude other diagnoses. Most biochemical investigations are normal. The blood creatine kinase level may be increased to two to three times its upper limit of normal in about 50 per cent of patients. In addition, a minor elevation in cerebrospinal fluid protein may be found and around 5 per cent have a paraprotein band in the serum.

The various differential diagnoses of motor neurone disease and relevant investigations are shown in Table 1.

### Table 1: Differential diagnosis of motor neurone disease

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Relevant investigations</th>
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<tbody>
<tr>
<td>Multilevel spinal spondylotic pathology</td>
<td>Magnetic resonance imaging (MRI)</td>
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<tr>
<td>Multifocal cerebrovascular disease</td>
<td>Computerised tomography or MRI imaging of the brain</td>
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<tr>
<td>Motor neuropathy</td>
<td>Nerve conduction studies</td>
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<tr>
<td>Myopathies</td>
<td>Electromyography (EMG), creatine kinase, C-reactive protein, muscle biopsy</td>
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<tr>
<td>Myasthenia gravis</td>
<td>Tensilon (edrophonium) test, acetylcholine receptor antibody titre, EMG</td>
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<tr>
<td>Syringomyelia/syringobulbia</td>
<td>MRI of spine/bone</td>
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<tr>
<td>Hyperthyroidism</td>
<td>Thyroid function tests</td>
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<tr>
<td>Lead or mercury toxicity</td>
<td>Heavy metal assays</td>
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<tr>
<td>Spinal muscular atrophy</td>
<td>Gene analysis for survival motor neurone mutations</td>
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<tr>
<td>Kennedy’s disease</td>
<td>Gene analysis for androgen receptor mutations</td>
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<tr>
<td>Post-polio syndrome</td>
<td>EMG</td>
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<tr>
<td>benign fasciculation syndrome</td>
<td>EMG</td>
</tr>
<tr>
<td>Hexosaminidase deficiency</td>
<td>Hexosaminidase A and B assays</td>
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**DISEASE PROGRESSION**

The average duration of survival in patients with motor neurone disease is two to three years, but the rate of progression varies. About 80 per cent of patients will survive five years and about 10 per cent will survive 10 years. The combined UMN and LMN features seen in the amyotrophic lateral sclerosis variant of motor neurone disease show steady progression over time. Bulbar weakness develops in about 50 per cent of these cases and respiratory weakness in almost all. Those patients with the bulbar palsy at onset will proceed to have limb involvement and although patients with the progressive muscular atrophy subtype have only LMN signs initially, almost all will eventually develop UMN signs. Poor prognostic factors include older age at onset and presentations with either bulbar or respiratory difficulties. The ultimate cause of death is usually respiratory failure, which can be accompanied by bronchopneumonia.

**PATHOGENESIS**

Current evidence suggests that the cell injury occurring in motor neurone disease probably reflects the complex interplay between multiple factors. Genetic factors, oxidative stress and imbalance of glutamate excitatory control of motor neurones are at present the main factors hypothesised to cause motor neurone injury. These processes may then be responsible for initiating a cascade of events that are responsible for damage to critical target proteins (such as neurofilaments) and organelles (such as mitochondria), ultimately resulting in motor neurone cell death.

**GENETICS**

Approximately 5 to 10 per cent of all cases are familial and usually inherited as an autosomal dominant trait. Rarely there have been reports describing pedigrees with autosomal recessive and X-linked inheritance. The single most important recent advance in understanding the pathogenesis of the disease was the discovery by Rosen et al in 1993 that certain forms of familial motor neurone disease were associated with point mutations in the gene encoding for the enzyme Cu/Zn superoxide dismutase (SOD1) located on chromosome 21. So far, more than 80 mutations have been discovered, representing 5 to 20 per cent of familial cases.

Under normal circumstances reactive oxygen species are generated in mitochondria as a by-product of electron transport and oxidative phosphorylation. SOD1 is a cystolic metalloenzyme that catalyses the conversion of these intracellular superoxide free radicals into hydrogen peroxide, which is in turn removed by the action of other free radical scavenging enzymes.

Originally it had been suggested that motor neurone degeneration might result from a reduction in the level of enzymatic activity of SOD1. However, there is now convincing evidence that this is not the case and that the mutant SOD1 protein exerts its detrimental effect through a “toxic gain of function”, rather than lack of function. Although the exact pathways leading to cell death of motor neurones in the presence of SOD1 mutations have not yet been fully identified, several hypotheses have been formulated. The most favoured is that the mutant SOD1 mishandles hydrogen peroxide and peroxynitrite leading to the formation of damaging hydroxy radicals and nitrotyrosine residues on intracellular proteins. Other hypotheses include the possibility that abnormal SOD1 causes intracellular protein aggregates which disrupt cellular functions or that the altered conformation of the mutant protein exposes the Cu/Zn motif which encourages the release of metal ions with resulting neurotoxicity.

The genetic alterations underlying the remaining 80 per cent of familial cases remain unknown. Occasional cases of sporadic motor neurone disease have been described that are associated with mutations in genes encoding a cytoskeletal protein (neurofilament heavy), a mitochondrial respiratory chain protein and a DNA repair enzyme (AP endonuclease). These are mostly isolated cases and the significance of these gene alterations remains unclear.

Recessive forms of juvenile motor neurone disease have been mapped to chromosome 2q and 15q, and autosomal dominant juvenile forms to chromosome 9q. Familial motor neurone disease associated with frontotemporal dementia has been linked to chromosome 9q.

**EXCITOTOXICITY**

Glutamate is the most abundant excitatory neurotransmitter in the nervous system and is essential for normal central nervous system function. During normal glutamergic neurotransmission, glutamate is released from the presynaptic terminal and passes across the synaptic cleft to activate postsynaptic receptors. The excitatory signal is terminated by removal of the glutamate from the synaptic cleft by glutamate reuptake transporter proteins located predominantly on perisynaptic glia.

It is known that excessive stimulation of glutamate receptors can injure neurones by mechanisms that include a deleterious rise in intracellular calcium and excessive free radical production. Timely removal of glutamate is therefore required if neuronal damage resulting from the excessive activation of cell surface glutamate receptors (or excitotoxicity, as the process has been termed) is to be avoided.

There is evidence suggesting that the expression and function of the major glial glutamate reuptake transporter protein EAAT2 (excitatory amino acid transporter 2) may be abnormal in motor neurone disease resulting in impaired glutamate removal and a damaging excitatory cascade occurring as a consequence. Cerebrospinal fluid glutamate levels appear to be elevated, at least in a proportion of patients. At present it remains uncertain as to whether any dysfunction of the glutamergic system in motor neurone disease is the primary pathophysiological process or is a secondary consequence of loss of motor neurones.

**OXIDATIVE STRESS**

Oxidative stress is damage caused to a cell by free radical species, and there is particular interest in the role of oxidative stress in the pathogenesis of motor neurone disease. Such interest developed after the discovery of the involvement of mutations in SOD1 in some familial cases, and SOD1 is an enzyme crucial for antioxidant defence. Studies of postmortem central nervous system tissues of motor neurone disease patients have shown biochemical changes to proteins that represent the effects of free radical damage.

In addition, postmortem studies have shown biochemical changes which have been interpreted as attempted compensatory responses to the presence of oxidative stress. Furthermore, fibroblasts cultured from the skin of patients with both familial and sporadic motor neurone disease have shown increased sensitivity to oxidative stress compared with those of controls. These findings all support the hypothesis that oxidative stress plays some role in the pathogenesis of motor neurone disease.

**OTHER PATHOGENIC HYPOTHESES**

In addition to the three main theories of motor neurone disease pathogenesis described above, there is emerging evidence that the cell death process can occur by an intracellular suicide programme known as apoptosis.

Further work has suggested that mitochondrial dysfunction may contribute to motor neurone injury. Other proposed factors include exposure to viral infections, involvement of immune-mediated mechanisms, environmental factors and exposure to toxic trace metals.
REFERENCES