Clinical aspects of motor neurone disease

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Abstract

Motor neurone disease (MND) is a disabling and ultimately fatal disease of the motor system, with few effective treatments. Considerable heterogeneity is observed in the clinical motor features of MND, with extra-motor manifestations now also recognized as part of the condition. Diagnosis remains clinical, with appropriate investigations to exclude mimics. The multidisciplinary team approach is at the centre of holistic management of patients and families and can improve survival and quality of life. Although the disease remains incurable, survival benefit has been observed with the use of non-invasive ventilation and riluzole. Recent identification of genetic causes of MND, particularly the *C9orf72* hexanucleotide repeat expansion, adds to the expanding knowledge on aetiology and pathogenesis. However, the challenge of elucidating the underlying causes and establishing effective disease-modifying therapies continues through active research. We review MND, focusing on clinical features, diagnosis and management.

Keywords Amyotrophic lateral sclerosis; disease modification: motor neurone disease; multidisciplinary care; non-invasive ventilation; riluzole

Key points

- Motor neurone disease (MND) is an uncommon neurodegenerative condition with a variable clinical course and median survival of 20–48 months
- Limb-onset amyotrophic lateral sclerosis, with mixed upper and lower motor neurone signs, is the most common type
- Diagnosis is clinical, with exclusion of mimics using appropriate investigations
- Multidisciplinary management, riluzole and non-invasive ventilation can improve survival and quality of life
- Expansions in the *C9orf72* gene are the most common identified genetic abnormalities, occurring in approximately 5% of sporadic cases of MND and 30% of familiar cases
- Overlap with other neurodegenerative conditions is recognized, with some patients displaying features of fronto-temporal dementia and Parkinsonism

Introduction

Motor neurone disease (MND) is a disabling and ultimately fatal neurodegenerative disease. Progressive paralysis and muscle atrophy occur following degeneration of corticospinal upper motor neurones (UMNs), and spinal cord and brainstem lower motor neurones (LMNs), with eventual death from respiratory failure.

Epidemiology

The lifetime risk of MND in the UK is 1 in 472 for women and 1 in 350 for men. Median survival is 20–48 months, meaning there are only approximately 5000 cases in the UK at any time. The incidence is highest in 55–75-year-olds, and onset <40 years of age uncommon.

Aetiology and pathogenesis

MND is thought to be caused by a complex interplay between genetic and exogenous factors. Pathogenic mechanisms to which motor neurones are particularly vulnerable, such as oxidative stress, glutamate excitotoxicity and mitochondrial dysfunction, are potential targets for new therapies. Around 5–10% of patients have a family history of MND, and a *C9orf72* gene mutation (a hexanucleotide repeat sequence expansion in an intronic region) has recently been identified in population studies. Abnormalities in this gene have been found in 12–46% of patients with a family history of MND and approximately 7–23% of sporadic cases.[1–3] This expansion has been associated with other neurodegenerative diseases, particularly fronto-temporal dementia and Parkinson's disease.[1–3]

Classification

MND can be classified into four main clinical phenotypes (Table 1).

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Clinical phenotypes of motor neurone disease

Phenotype	Features
ALS	75% of all cases Limb onset with mixed UMN and LMN clinical features Average survival 2–5 years Men > women (3:2), incidence peaking around 75–79 years
Progressive bulbar palsy	20% of all cases Bulbar (LMN) and/or corticobulbar (UMN) palsy onset Poorer prognosis
Progressive muscular atrophy	5% of cases Pure LMN signs at onset, can later develop UMN signs Men >> women (5:1) May be associated with slower disease progression
Primary lateral sclerosis	Pure UMN signs at onset at onset, lower limbs often affected first 0.5% of cases 50% progress to ALS phenotype Better prognosis, can have normal life expectancy

ALS, amyotrophic lateral sclerosis.

Table 1

Presenting symptoms

The most common presentation is painless, often distal and asymmetrical weakness, wasting or fasciculation of limb muscles. Although the disease is relentlessly progressive, patients can report fluctuations as a result of fatigue or loss of compensatory strategies.

Lower limb onset disease can present with difficulty walking, unsteadiness, stiffness or foot drop.

Upper limb onset disease can present with loss of functional hand dexterity, poor grip or proximal arm weakness.

Bulbar-onset MND can present with changes in vocal quality or volume, dysphagia or excessive salivation.

Respiratory-onset MND is uncommon. Symptoms include breathlessness, orthopnoea and hypercapnic features from overnight hypoventilation, such as morning headaches, daytime somnolence or loss of appetite.

Extra-motor manifestations of MND are increasingly recognized: overt fronto-temporal dementia affects approximately 5% of patients, with more experiencing minor cognitive difficulties or emotional lability and a small number having Parkinsonism. Sensory features, eye movement abnormalities, severe pain and sphincter involvement may suggest an alternative diagnosis.

Examination

Clinical signs on examination are often more widespread than the symptoms, and the presence of UMN and LMN in the same area is suggestive of MND. UMN signs include increased tone, brisk reflexes and extensor plantar responses. LMN signs include muscle wasting, fasciculations and reduced or absent reflexes. Examination of the small muscles of the hands can reveal early wasting of the first dorsal interossei and finger extensors with preserved finger flexion (Figure 1). Bulbar findings include dysarthria and dysphonia and tongue weakness, wasting or fasciculations (LMN). Tongue spasticity, brisk jaw jerk and emotional lability suggest UMN corticobulbar (or pseudobulbar) palsy.

Assessment should note the ability to perform activities of daily living, cough, swallow and respiratory function with bedside testing including forced vital capacity, transdermal arterial oxygen and carbon dioxide concentrations and the Edinburgh Cognitive and Behavioural ALS Screen.

Making the diagnosis

Diagnosis remains clinical, using investigations to exclude mimics. Patients can present to orthopaedics, ear, nose and throat and respiratory medicine as well as neurology; identification of neurological signs can be a clue in diagnosis. Mimics affecting LMNs include mononeuritis multiplex, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, nerve entrapment disorders, spinal muscular atrophy and post-polio syndrome. X-linked Kennedy's syndrome, caused by a trinucleotide repeat expansion in the androgen receptor gene, has a better prognosis than MND with a slower, LMN spinal and bulbar disease that can be associated with diabetes mellitus, gynaecomastia and testicular atrophy.

Muscle disorders should be considered, particularly inclusion body myositis, which causes asymmetrical weakness and wasting; and, in contrast to the pattern of weakness in MND, the quadriceps and finger flexors are characteristically involved. Non-progressive benign cramp–fasciculation syndrome presents with isolated cramps and fasciculations without other neurological signs. Structural, infective or inflammatory intracranial or spinal pathology and hereditary spastic paraparesis cause pure UMN signs, whereas cervical radiculomyelopathy, syringomyelia/bulbia and dual pathologies can present with mixed UMN and LMN signs. Brainstem or oropharyngeal lesions, myasthenia gravis and oculopharyngeal muscular dystrophy should be considered in bulbar presentations.

Investigations

Nerve conduction studies and electromyography can identify LMN pathology and muscle disorders, whereas magnetic resonance imaging of the brain and spine is indicated with clinical UMN signs. Blood tests should exclude hyperthyroidism, hyperparathyroidism, HIV and Lyme disease, and lumbar puncture should be considered in atypical cases to exclude inflammatory or infiltrative disease. Genetic testing should be considered to diagnose Kennedy's syndrome and individuals with MND with relevant clinical features (such as young onset, or features or family history of neurodegenerative disorders). Next-generation sequencing of a panel of genes can aid diagnosis, but genetic counselling is important given the impact of the diagnosis on the family and potential family planning options such as pre-implantation diagnosis.