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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 unfortunately 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 both survival and quality of life. Although the disease remains incurable, a survival benefit has been observed with the use of non-invasive ventilation and riluzole. Recent identification of genetic causes of MND, particular the *C9ORF72* hexanucleotide repeat expansion, adds to the expanding knowledge regarding aetiology and pathogenesis. However, the challenge to elucidate underlying causes of MND and establish effective disease-modifying therapies continues through active research. We provide a comprehensive review of MND, focusing on clinical features, diagnosis and management.

Keywords

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

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 women and higher - 1 in 350, in men. The median survival is only 20-48 months (1) meaning there are only approximately 5000 cases in the UK at any one time. (2) Incidence is highest in 55-75-year olds and onset below the age of 40 years uncommon. (2)

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. 5-10% of patients have a family history of MND, but recently, a C9ORF72 gene mutation (a hexanucleotide expansion repeat sequence in an intronic region of the gene) has been found in population studies to be present in 12-46% of cases with a family history and approximately 7-23% of sporadic cases. (3-5) This expansion has been associated with other neurodegenerative diseases: in particular fronto-temporal dementia and Parkinson's disease. (3-5)

Classification

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

Presenting symptoms

The most common presentation is of painless, often distal and asymmetrical weakness, wasting or fasciculation of limb muscles. Whilst the disease is relentlessly progressive, patients may report fluctuations due to fatigue or loss of compensatory strategies.

Lower limb onset causes difficulty in walking, unsteadiness, stiffness or foot-drop.

Upper limb onset causes loss of functional hand dexterity, poor grip or proximal arm weakness.

Bulbar-onset MND can present with change in the quality or volume of voice, dysphagia or excessive salivation.

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

Extra-motor manifestations of MND are becoming increasingly recognised: overt fronto-temporal dementia affects approximately 5% of patients with a larger number experiencing minor cognitive difficulties or emotional lability and a small number having Parkinsonism. (6) Atypical findings such as sensory features, eye movement abnormalities, severe pain and sphincter involvement may suggest an alternative diagnosis.

Examination

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

Assessment should also note the patient's abilities to perform activities of daily living, cough, swallow and respiratory function with bedside testing including force vital capacity (FVC), transdermal arterial oxygen and carbon dioxide levels and the Edinburgh Cognitive and Behavioural ALS Screen (ECAS).

Making the diagnosis

Diagnosis remains clinical, using investigations to exclude mimics. Patients may present to other specialties including orthopaedics, ENT and respiratory medicine: identification of neurological signs may be a clue to the diagnosis. Mimics affecting the LMN include mononeuritis multiplex, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, nerve entrapment disorders, spinal muscular atrophy and post-polio syndrome. The X-linked disorder Kennedy's syndrome, caused by a trinucleotide repeat expansion in the androgen receptor gene, and has a better prognosis than MND with a slower, LMN spinal and bulbar disease, which may be associated with diabetes, gynaecomastia and testicular atrophy.

Muscle disorders should be considered, particularly inclusion body myositis, which causes asymmetrical weakness and wasting, although, in contrast to the typical pattern of weakness in MND, the quadriceps and finger flexors are characteristically involved. The 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 whilst 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 those with MND with relevant clinical features (such as young onset, or with features of, or a family history of neurodegenerative disorders). Next-generation sequencing of a panel of genes can aid diagnosis, but genetic counseling should

be considered given the impact of the diagnosis on the family and potential family planning options such as pre-implantation diagnosis.

Giving the diagnosis

Sensitive delivery of the diagnosis of MND, combining honesty without destruction of hope, can have a positive impact on patients. The doctor should explain the incurable nature of the disease, its variable but unpredictable prognosis and a positive emphasis on the treatment and support available, including the role of the multidisciplinary team (MDT). Early and ongoing follow-up should be arranged with the hospital and community MDT.

Management

Multidisciplinary team

Care by a specialist MND teams is associated with a better survival and quality of life (7). The team should include nurse specialists, physiotherapists, occupational, speech and language therapists and dieticians, whilst involvement from respiratory medicine, gastroenterology and palliative care may be required later in the disease course. The Motor Neurone Disease Association charity provides support to patients and families in the UK. Along with symptom management and psychosocial support, access to mobility and communication aids, social care and financial assistance is vital.

Respiratory support

Respiratory failure is often insidious and presents with symptoms of daytime somnolence, disturbed sleep, morning headaches, loss of appetite or reduced exercise tolerance. Loss of cough and bulbar function can result in aspiration and pneumonia and is a common cause of death. Use of non-invasive ventilation (NIV) improves survival by an average of 7 months with preserved quality of life (8) whilst physiotherapy, cough assist devices, nebulisers and suction machines can aid mucous clearance. A recent UK study found that diaphragmatic pacing as an adjunct to NIV appeared detrimental and was associated with shorter survival. (9)

Nutritional support

Weight loss, choking episodes, aspiration and tiring at mealtimes may indicate the need for supplementary feeding. Percutaneous endoscopic gastrostomy (PEG) insertion can be adapted for frailer patients or those with respiratory failure in whom the procedure presents a higher risk (10). Options should be discussed early, as evidence suggests that the best outcomes are achieved if PEG insertion occurs before major loss of body weight or marked deterioration in respiratory function. (10)

Pharmacological treatments

Riluzole is the only drug licensed for treatment of the ALS form of MND and modestly prolongs median survival by approximately 3 months. (11) Trials of other multiple other potential neuroprotective agents such as lithium and dextramipexole have failed to show benefit.

Symptomatic therapies: the MDT approach to symptoms usually involves both pharmacological and non-pharmacological strategies. Table 2

Prognosis

The median survival for ALS is 20-48 months, but 10% of patients with ALS live longer than 10 years and patients with primary lateral sclerosis may have a normal life expectancy. (1) Poor prognostic indicators include older age and bulbar- or respiratory-onset. Patients may wish to discuss end-of-life issues and make advanced directives at any time in the disease.

Conclusion

As research continues to advance our understanding of MND pathogenesis, identification of new therapeutic targets will assist in creating novel treatments, with the ultimate goal of arresting the progression of MND. In the meantime, the holistic MDT approach has improved survival and quality of life of patients and carers living with the disease.

Key points

- MND is an uncommon neurodegenerative disease with a variable phenotype
- There are approximately 5 000 people in the UK with MND, peak onset being 55-75 years
- It has a highly variable clinical course, but a median survival of 20-48 months
- Limb-onset amyotrophic lateral sclerosis, with mixed upper motor neurone and lower motor neurone signs, is the most common type
- Diagnosis is clinical, with exclusion of mimics using appropriate investigations
- Management requires a multidisciplinary approach, which can improve survival and quality of life
- Riluzole and non-invasive ventilation also improve survival.
- Whilst familial disease is uncommon, advances in understanding the genetics of MND have been made, with expansions in the C9ORF72 gene now being commonest identified genetic abnormality, occurring in 10% of all cases of MND.
- There is an increasingly recognised overlap with other neurodegenerative conditions with some patients displaying features fronto-temporal dementia and Parkinsonism.

Table 1**Clinical phenotypes of motor neurone disease**

Phenotype	Features
Amyotrophic lateral sclerosis (ALS)	75% of all cases
	Limb onset with mixed UMN and LMN clinical features
	Average survival 2-5 years
	Men >women (3:2)
Progressive bulbar palsy (PBP)	20% of all cases
	Bulbar (LMN) and/or pseudobulbar (UMN) palsy onset
	Poorer prognosis
Progressive muscular atrophy (PMA)	5% of cases
	Pure LMN signs at onset, may develop UMN signs later
	Men>>women (5:1), onset commonly <50 years old
	May be associated with slower disease progression
Primary lateral sclerosis (PLS)	Pure UMN signs at onset at onset, lower limbs often affected first
	0.5% of cases 50% progress to ALS phenotype
	Median onset 50 years old
	Better prognosis, may have normal life expectancy

Table 2

Symptomatic therapies in motor neurone disease

Symptoms	Pharmacological therapy	Notes
Cramps and fasciculations	Quinine 200–300 mg at night Carbamazepine start at 100 mg daily	Titrate doses to response
Spasticity	Baclofen start at 5 mg bd-tds Dantrolene start at 25 mg daily Tizanidine start at 2 mg daily	Cautious titration: low tone may worsen mobility Treat worsening factors e.g. pain, constipation Physiotherapy
Excessive saliva	Hyoscine patch 0.5–1 mg every 3 days Amitriptyline start at 10 mg at night Atropine 1% eye drops bd-tds	Suction machines In severe cases botulinum toxin to salivary glands or hyoscine syringe driver Thinning saliva may worsen thick respiratory secretions
Poor cough /respiratory secretions	Carbocysteine 250–750 mg tds Nebulised saline	Cough-assist and suction devices Adequate fluid intake
Emotional lability	SSRIs (e.g. citalopram 10mg) Amitriptyline start at 10 mg at night	Psychological support Educate about cause of symptoms
Constipation	Lactulose / docusate / movicol	Review drug adverse effects Check adequate fluid and fibre intake
Dyspnoea	Oral morphine start at 2.5 mg 6-hourly Nebulised morphine 5 mg Lorazepam sublingual 0.5–2 mg Diamorphine in late stages	Pre-emptive palliative prescribing Increase use of NIV Address anxiety and fears Attention to sleeping position
Paroxysmal choking/ laryngospasm	Lorazepam sublingual 0.5–2 mg	Careful positioning Suction/NIV may help

SSRIs, selective serotonin reuptake inhibitors; NIV, non-invasive ventilation.

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