Clinical aspects of motor neurone disease

Ceryl A Harwood
Christopher J McDermott
Pamela J Shaw

Abstract

Motor neurone disease (MND) is a disabling and ultimately fatal disease of the motor system, with unfortunately few effective treatments. With a relatively uniform annual incidence worldwide of approximately 2 per 100,000, there are about 5000 cases of MND in the UK at any one time. Considerable heterogeneity is observed in the clinical motor features of MND, with extra-motor manifestations now also recognized as part of the condition. In the absence of specific disease markers, diagnosis remains clinical, with appropriate investigations to exclude mimics. Patient management is challenging but can be optimized with regular specialist follow-up, open but sympathetic communication and a multidisciplinary team approach. Advances in the holistic care of patients living with MND have considerably improved the management of physical, social and psychological symptoms. Although the disease remains incurable, a survival benefit has been observed with some therapies, particularly non-invasive ventilation and riluzole, now licensed for MND and recommended by NICE guidelines. Recent identification of genetic causes of MND 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 condition of the motor nervous system. 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.

Ceryl Harwood *MBChB MRCP is a Clinical Research Fellow working at Sheffield Institute for Translational Neuroscience, University of Sheffield, UK. Competing interests: none declared.*

Christopher J McDermott *MBChB FRCP PhD is a Clinical Senior Lecturer and Honorary Consultant Neurologist at the University of Sheffield and Royal Hallamshire Hospital, Sheffield, UK. His research interests are neuromuscular disorders including motor neurone disease. Competing interests: none declared.*

Pamela J Shaw *MBBS FRCP MD FMedSci is Professor of Neurology and Consultant Neurologist at the University of Sheffield and Royal Hallamshire Hospital, Sheffield, UK. She is also Director of the Sheffield Institute for Translational Neuroscience. Competing interests: none declared.*

What's new?

- Considerable advances in understanding the genetics of motor neurone disease (MND) have been made within the last year
- Mutations in the C9ORF72 gene are now highlighted as the commonest genetic cause of familial and sporadic MND
- Clinical, pathological and genetic overlap with other neurodegenerative conditions, in particular frontotemporal dementia, is becoming more apparent
- NICE has published new clinical guidelines for non-invasive ventilation use in MND

Epidemiology

MND is relatively rare, with approximately 5000 cases in the UK at any one time. A fairly uniform annual incidence of about 2/100,000 is seen worldwide, although high-incidence foci are observed on the Western Pacific island of Guam and the Kii Peninsula of Japan.[1,2,3] Increasing age is a risk factor, with incidence highest in 55–75-year olds, and onset below the age of 40 years uncommon.[2,4] The male to female ratio is about 3:2.

Aetiology and pathogenesis

The aetiology of MND is not fully understood. However, a complex interplay between genetic and exogenous factors is thought to underlie the disease. Most cases are sporadic, with only 5–10% being familial. Apart from an earlier age of onset, familial MND is clinically indistinguishable from sporadic disease. Approximately 20% of familial cases are associated with mutations in the copper/zinc superoxide dismutase (SOD-1) gene.[5] However, the recently identified C9ORF72 gene mutation (a hexanucleotide expansion repeat sequence in an intronic region of the gene) has been reported to be associated with approximately 40% of familial cases and up to 21% of sporadic cases within multiple international populations, and therefore represents the commonest gene mutation for both forms of MND.[6–8] Other familial genetic variants of lower prevalence include changes in TAR DNA binding protein (TDP-43),[9] fused in sarcoma (FUS),[10] valosin-containing protein (VCP),[11] and angiogenin (ANG).[12] Beyond the C90RF72 mutation, genomic studies of sporadic MND have produced inconsistent evidence, although several other susceptibility genes have been implicated, including vascular endothelial growth factor (VEGF) and survival motor neurone 1.[13,14]

Many potential environmental and lifestyle risk factors have also been proposed, including physical activity, smoking, mechanical and electrical injury, exposure to neurotoxins and certain occupations, including farming, military service and professional football. However, none has been confirmed unequivocally.

In conjunction with genetic susceptibility, multiple pathogenic mechanisms are known to contribute to neuronal degeneration in MND, including oxidative stress, glutamate excitotoxicity, mitochondrial dysfunction, defects of axonal transport and perturbations of glial cell function, with selective vulnerability of motor neurones to many of these processes.[15,16,17]

Classification

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

Presenting symptoms

The early symptoms of MND are varied. The most common presentation is of spontaneous, painless weakness and/or wasting of limb muscles, which is often distal and asymmetrical, and can be focal.

Lower limb onset manifests as difficulty in walking, unsteadiness, foot-drop, a tendency to stumble or heaviness and/or stiffness of one or both legs.

Upper limb onset may cause loss of functional hand dexterity, poor grip or proximal arm weakness. Patients may also notice muscle wasting, particularly in the hands, or fasciculations, especially of the large proximal limb muscles.

Bulbar-onset MND usually presents with dysarthria or dysphonia with a nasal, hoarse or tight voice. Early dysphagia is more prominent with liquids than with solids, although it is rare without speech disturbance.

Respiratory-onset MND is very uncommon. Symptoms include breathlessness, orthopnoea or hypercapnic features from overnight hypoventilation such as fatigue, reduced exercise tolerance, hypersomnolence and morning headaches.

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 50% progress to involve bulbar muscles Men>women (3:2)
Progressive bulbar palsy (PBP)	20% of all cases Bulbar and/or pseudobulbar palsy onset Most common in elderly women 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)	0.5% of cases Pure UMN signs at onset, lower limbs often affected first 50% progress to ALS phenotype Median onset 50 years old Better prognosis, survival >10 years common
Segmental variants (rare)	
Flail arm syndrome[18]	Predominant proximal LMN involvement of both arms, also known as 'man in a barrel syndrome'
Flail leg syndrome	Predominant LMN weakness of legs

UMN, upper motor neurones; LMN, lower motor neurones.

Table 1

Examination

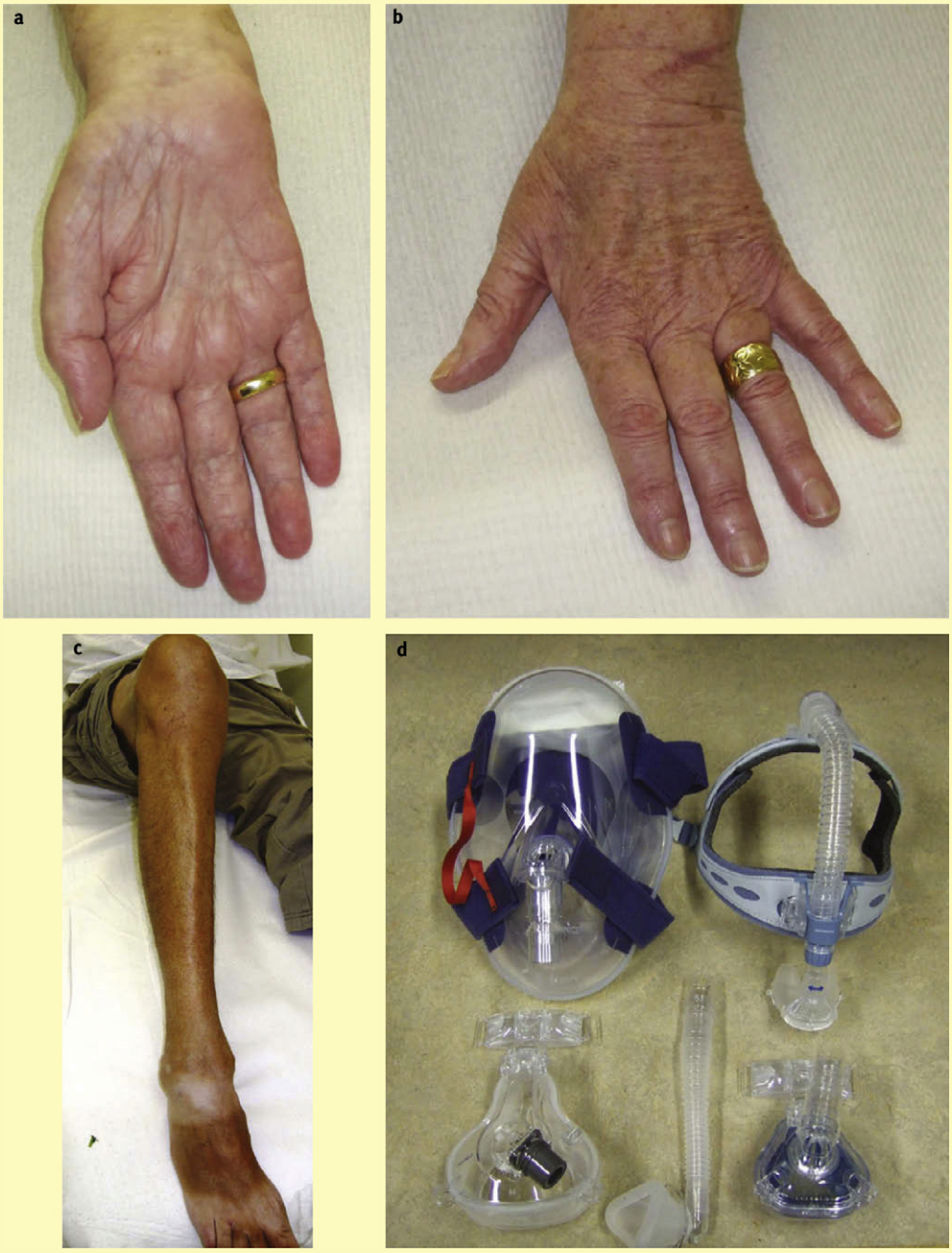
The clinical signs on examination are frequently more widespread than the patients' symptoms. Any combination of motor neurone signs may be elicited, although concurrent UMN and LMN signs, particularly if in the same limb and in the absence of sensory impairment or pain, should prompt consideration of MND. UMN signs may include hypertonicity, brisk reflexes and extensor plantar responses. LMN signs comprise muscle wasting, fasciculations and reduced or absent reflexes.

Wasting of tibialis anterior and small muscles of the hands, particularly the thenar eminence and first dorsal interosseous, is typical (Figure 1a, b and c). Concurrent weakness of wrist and finger extensors may cause a claw-like hand. Foot-drop is common because of weak ankle dorsiflexion. Bulbar findings include tongue weakness with spasticity and/or wasting and fasciculations. In the presence of UMN bulbar signs, the jaw jerk is likely to be pathologically brisk and emotional lability may be present.

Disease progression

MND progression is variable and unpredictable, although typically symptoms increase in severity and distribution. Weakness of posterior neck and thoracic paraspinal muscles is common. Approximately half of limb-onset patients with amyotrophic lateral sclerosis (ALS) develop bulbar weakness. Patients may lose the ability to communicate verbally, swallow safely or manage their own saliva, with subsequent weight loss, risk of aspiration, drooling and distressing coughing spells. Although patients may not recognize early features of respiratory insufficiency, as the disease advances orthopnoea and breathlessness become more prominent.

It is now recognized that MND is a multisystem degenerative disorder with motor neurones showing the greatest vulnerability to the pathological process. Extra-motor manifestations of MND may include minor sensory symptoms, mild cognitive impairment, dysautonomia and emotional lability. Concurrent overt frontotemporal dementia affects approximately 5% of patients. However, clinical and pathological overlap between the two conditions is becoming increasingly apparent, particularly in view of recent knowledge that genetic mutations in C9ORF72 may underlie both motor neurone degeneration and frontotemporal dementia.[6–8] Atypical findings such as diffuse sensory features, marked cognitive decline, eye movement disorder, severe pain and sphincter involvement should prompt consideration of an alternative diagnosis.



Wasting of the thenar, hypothenar **a** and dorsal interossei **b** muscles of the hand. Muscle wasting is a common finding in MND, although it may be focal in the early stages and remain asymmetric throughout the disease. **c** Wasting of the tibialis anterior muscle of the leg is another common sign in MND patients on examination. **d** A wide choice of NIV masks are available for use by MND patients, including nasal, full-face and total-face masks.

Figure 1

Making the diagnosis

Diagnosis remains clinical, with appropriate investigations to exclude mimics. The El-Escorial diagnostic criteria provide guidance, although these were produced as a research tool and their usefulness in clinical practice has been questioned.[19]

Differential diagnosis

The differential diagnosis for MND depends on the signs present. Conditions that can present with an LMN phenotype include mononeuritis multiplex, chronic inflammatory demyelinating polyneuropathy, nerve entrapment disorders, spinal muscular atrophy and post-polio syndrome. Multifocal motor neuropathy with conduction block is a treatable neuropathy, which can closely resemble MND, presenting with progressive distal limb weakness and atrophy, often with fasciculations and cramps. Careful nerve conduction studies (NCS) will identify conduction block. The X-linked disorder of Kennedy's syndrome, caused by a CAG (cytosine, adenine, guanine) trinucleotide repeat expansion in the androgen receptor gene, presents with LMN spinal and bulbar features, which may be associated with diabetes, gynaecomastia and testicular atrophy. Myopathies should also be

considered, particularly inclusion body myositis, which causes insidious 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.

Pure UMN features may denote structural intracranial or spinal pathology, infective or inflammatory myelopathies or hereditary spastic paraparesis. 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 of MND.

Investigations

NCS and electromyography (EMG) are valuable in excluding peripheral neuropathies and myopathies. EMG can demonstrate the extent of subclinical disease, with active and chronic denervation and re-innervation supporting a diagnosis of MND. Magnetic resonance imaging (MRI) of the brain and spine is indicated with clinical UMN signs. Few blood tests are helpful, although hyperthyroidism, hyperparathyroidism, HIV and Lyme disease can all mimic MND. Serum creatine kinase is often elevated up to four times the normal level, although higher values may suggest an alternative diagnosis. Lumbar puncture should be considered in atypical cases to exclude inflammatory or infiltrative disease. Genetic testing for Kennedy's syndrome is available.

Giving the diagnosis

Delivering the diagnosis of MND is challenging. A private setting with both personal and professional support present and adequate time for discussion is essential. Important features to address in an honest but sympathetic manner include an explanation of the incurable nature of the disease, its variable but unpredictable prognosis, the treatments used, the medical and psychological support available, and the role of the multidisciplinary team (MDT). Early and ongoing follow-up should be arranged.

Management

Effective disease-modifying treatments for MND are limited, although therapies that prolong life and improve symptom control are available.

Multidisciplinary team

Optimal management considers the physical, social and psychological aspects of the disease with active involvement of patients and carers. A coordinated multidisciplinary approach using MND nurse specialists, physiotherapists, occupational, speech and language therapists, and dieticians is effective in alleviating symptoms and maintaining a good quality of life. Input from physicians in respiratory medicine, gastroenterology and palliative care may be required. MND charities and support groups provide additional assistance.

Useful interventions include ankle-foot orthoses, neck supports, mobility devices, mobile arm supports and speech aids such as light-writers. In advanced disease, chest physiotherapy and passive limb exercises can be taught to carers to reduce complications such as pneumonia and joint contractures. Bulbar involvement necessitates careful monitoring of swallowing ability and nutrition (malnutrition and weight loss are associated with shorter survival)[20] with provision of advice regarding swallowing techniques and food intake.

Respiratory support

The use of non-invasive ventilation (NIV) for respiratory muscle impairment signifies an important development in MND care (Figure 1d). National Institute for Health and Clinical Excellence (NICE) guidelines, published in 2010, now support its use. Beyond favourable effects on survival and quality of life, NIV relieves symptoms of hypoventilation. However, it may be less effective if bulbar function is poor.[21,22] NIV is initially used at night, although advanced disease may necessitate daytime use. The presence of respiratory symptoms, nocturnal desaturation, hypercapnia, and vital capacity (FVC) less than 50% of expected are often used to guide NIV initiation, although earlier intervention may improve survival.[23]

Nutritional support

Continued weight loss, symptoms of aspiration, distressing choking episodes or prolonged tiring at mealtimes may indicate the need for supplementary enteral feeding. Although percutaneous endoscopic gastrostomy (PEG) is widely used, an increasingly preferred option, particularly if respiratory function is poor, is percutaneous radiological insertion of gastrostomy, which can be sited without sedation. However, both procedures are invasive and are not always tolerated by patients. If bulbar symptoms are present, options should be discussed early. Evidence suggests that PEG insertion whilst FVC higher than 50% expected achieves the best outcomes.[24]

Pharmacological treatments

Riluzole: the only drug licensed for treatment of the ALS form of MND, and recommended by NICE, is riluzole. A recent Cochrane review update concluded that riluzole probably prolongs median survival by approximately 3 months,[25] although greater benefits have been suggested. In practice, it is commonly prescribed for all MND phenotypes at diagnosis at a dose of 50 mg twice a day, but should always be initiated by a neurologist with experience in MND. Regular liver enzyme monitoring is advisable, monthly for the first 3 months, then 3-monthly for 9 months, then annually. Though a rare adverse effect, neutropenia should be considered if a patient becomes febrile on riluzole. Riluzole should be avoided in liver and/or renal impairment and if the patient is pregnant or breast-feeding, Because of variability in disease progression, response is almost impossible to determine and riluzole is usually continued indefinitely unless adverse effects prove unacceptable.

Previous trials of agents that modify pathogenic mechanisms in MND, including the recent international trials of lithium, have failed to demonstrate effective clinical outcomes. Despite this, antioxidant vitamins are often prescribed because of their low cost, safety and tolerability.

Symptomatic therapies in motor neurone disease

Symptoms	Pharmacological therapy	Others
Cramps and fasciculations	Quinine 200—300 mg at night	Titrate doses to response
	Carbamazepine start at 200 mg daily	Physiotherapy may help
	Diazepam start at 2 mg three times daily	
Symptoms due to spasticity	Baclofen start at 5 mg twice daily	Cautious titration as low tone may worsen mobility
	Dantrolene start at 25 mg daily	Rule out exacerbating causes
	Tizanidine start at 2 mg daily	
Drooling/sialorrhoea	Hyoscine patch 0.5—1 mg every 3 days	Saliva control techniques
	Amitriptyline start at 10 mg at night	Parotid gland irradiation
	Atropine 300—600 μg two or three times daily	Botulinum toxin to salivary glands
Difficulty coughing/clearing respiratory secretions	Carbocysteine 250—750 mg three times daily	Adequate fluid intake
	Nebulized saline	Cough-assist devices
		Suction device
Emotional lability/pseudobulbar affect	Amitriptyline start at 25 mg at night	Psychological support
	SSRIs (e.g. citalopram)	Educate about cause of symptoms
Constipation	Lactulose 10—20 ml twice daily	Review drug adverse effects
	Docusate 100—200 mg once or twice daily	Check adequate fluid and fibre intake
	Movicol® 1—2 sachets once or twice daily	
Dyspnoea	Oral morphine start at 2.5 mg 6-hourly	Titrate carefully to symptoms
	Nebulized morphine 5 mg	Address anxiety and fears.
		Breathing space kit (MNDA)
	Lorazepam sublingual 0.5—2 mg	Attention to sleeping position
	Diamorphine in late stages	NIV
Paroxysmal choking/laryngospasm	Lorazepam sublingual 0.5—2 mg	Careful positioning

SSRIs, selective serotonin reuptake inhibitors; MNDA, Motor Neurone Disease Association; NIV, non-invasive ventilation.

Table 2

Symptomatic therapies: many symptoms experienced in MND respond to pharmacological interventions (Table 2). However, they should be combined with MDT care as the two often complement each other and can reduce the need for some medications.

Prognosis

Prognosis is variable, ranging from a few months to over 10 years, although the majority of patients survive only 2—3 years from diagnosis. Poor prognostic indicators include old age and bulbar- or respiratory-onset MND. Most patients die peacefully in their sleep due to hypercapnia. As disease advances, patients may wish to plan for and discuss end-of-life issues. Palliative care services can provide terminal symptom control and hospice care. Advanced directives are increasingly favoured.

Conclusion

MND is a distressing condition with few effective therapies and limited prognosis. However, the modern holistic management approach has improved the quality of life of patients and carers living with MND, and new interventions have achieved some survival benefit. 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. ◆

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Practice points

- MND is uncommon, with a relatively uniform annual incidence of about 2 per 100,000 worldwide
- Peak age of onset is between 55 and 75 years, although adults of all ages can develop MND
- Presentation is varied. 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
- Optimal management requires a multidisciplinary approach with involvement of patients and carers. Riluzole and NIV are the only interventions with established survival benefit

