Neurology – 1

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Motor neuron disease and its management

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Motor neuron disease (MND) is a progressive neurodegenerative condition, affecting pyramidal neurons of the corticospinal tract (upper motor neurons (UMN)), brainstem motor nerve nuclei and spinal cord anterior horn cells (lower motor neurons (LMN)). Clinical presentation varies, according to the site(s) affected and the relative balance between UMN and LMN signs (see Table 1). The term 'amyotrophic lateral sclerosis' (ALS) is widely used interchangeably with 'motor neuron disease', though ALS is strictly the combination of UMN and LMN degeneration. Both terms are used to encompass limb and bulbar onset forms of the disease. Hence, ALS, progressive bulbar palsy and progressive muscular atrophy (the latter most often an LMN variant of the syndrome) all fall under the rubric of ALS/MND. The rate of progression also varies, but median survival for patients with limb onset (75% of total) is 3.5 years and with bulbar onset (25%) 2.5 years[1].

Although the clinical features of MND are predominantly or entirely motor, the disease is not confined to motor neurons alone. Psychological[2], neuroimaging[3] and pathological studies[4] demonstrate the involvement of other central nervous system regions. Furthermore, well recognised 'MND-plus' syndromes are seen in which other features develop in parallel with the motor disorder (Table 1).

This review focuses on the diagnosis and management of MND. The problems caused by the disease vary, but in all cases there is progressive impairment of limb, bulbar and respiratory function. Unfortunately, much current practice lacks supportive evidence – well designed, adequately powered clinical trials are a recent development in MND. Most studies have focused on attempts to delay disease progression, rather than to evaluate symptom control. Some therapies are of proven efficacy in situations (eg spasticity) which are akin, but not identical, to those that arise in MND. Particular areas of uncertainty will be highlighted.

Table 1. Classification of motor neuron diseases (MND).

	Signs	
	UMN	LMN
Motor syndromes comprising MND		
Amyotrophic lateral sclerosis (in current usage, this includes progressive bulbar palsy)	Yes	Yes
Progressive muscular atrophy	No	Yes
Primary lateral sclerosis	Yes	No
MND-plus syndromes		
(other clinical features developing in parallel with MND; these may occur in combination (classified as (5))		
• extrapyramidal signs		
• cerebellar signs		
• dementia		
• autonomic nervous system involvement		
• objective sensory abnormalities		

Diagnosis

The hallmark of typical MND is combined and widespread UMN and LMN signs, without sensory loss, eye movement disorder, sphincter dysfunction or clinical involvement of other systems (Table 2). Research diagnostic criteria have been defined[5]. In practice, patients who, by these criteria, have 'possible' MND nearly always have the condition, though false positive diagnoses comprised 8% of one series[6]. There are no specific tests, but detailed investigations are of use in excluding other conditions. Careful clinical assessment is the keystone of diagnosis.

Electrophysiological investigations are required in all cases to provide evidence of denervation and reinnervation without motor nerve conduction block. Additionally, particularly when LMN signs are cranial to UMN signs or when sensory symptoms complicate the presentation, magnetic resonance imaging (MRI) is indicated to exclude compression or infiltration of the spinal cord or roots. T2-weighted MRI of the brain occasionally demonstrates increased signal along the corticospinal tracts, but this is a non-specific finding. Creatine kinase is often raised by up to 3–4 times normal.

Muscle biopsy can be helpful when electromyographic changes are either equivocal or suggestive of a myopathic process. Inclusion body myositis in particular should be considered. DNA analysis will identify Kennedy's disease, and antiganglioside (anti-GM1) antibody testing aids the diagnosis of multifocal motor neuronopathy (MFMN) with conduction block. Anti-GM1 antibodies and conduction block are often difficult to demonstrate in MFMN but, if there is a reasonable suspicion of this potentially treatable disorder, a therapeutic trial of intravenous immunoglobulin (0.4 g/kg body weight/day for 5 days) may be considered. Quantitative myometry and clinical assessment before and after treatment are essential to document any response.

The only proven cause of MND is mutation of the gene encoding the enzyme copper/zinc superoxide dismutase (SOD1). This has been found in 3–4% of all cases: in about 20% of the approximately 5% of MND patients with a family history and 3% of sporadic cases[7]. To date, over 60 different mutations have been identified. SOD1 screening is available, but counselling is mandatory before predictive testing is undertaken.

Key Points

Diagnosis:

- progressive, mixed upper and lower motor neuron signs supported by electrophysiological tests are the hallmark of motor neuron disease (MND)
- other features may raise the possibility of a mimic condition or MND-plus syndrome

Management:

- multidisciplinary care is essential actively to anticipate worsening disability and pre-empt avoidable problems
- good communication between all those involved is vital
- all interventions should be considered as to their possible side effects and whether they offer true benefit to the patient
- do not neglect treatment of other diseases

Respiratory care:

- non-invasive ventilation is not suitable for all patients, but can offer major improvements in symptoms and quality of life

Care of bulbar dysfunction:

- regular speech and language therapy (SALT) assessment, early attention to diet and consideration of gastrostomy, treat sialorrhoea as necessary

Care of limb dysfunction:

- occupational therapy and physiotherapy, plus specialised units
- symptomatic agents for spasticity, cramps and fasciculations

Psychological:

- treat depression in patients and carers, consider respite care

Disease-modification:

- small but definite effect of riluzole
- possible benefit from gabapentin

End of life:

- consider early referral to palliative care service

Management

General principles

MND patients should be cared for by a multidisciplinary team experienced in the care of the disease (Table 3). Several regions in the UK have specialised MND care and research centres, with close links to colleagues in hospital and the

Table 2. Diagnosis of motor neuron disease (MND).

Suggested guidelines for confident clinical diagnosis of MND:

- combined UMN and LMN signs in one or more regions: cranial, cervical (upper limb), lumbosacral (lower limb)
- progression over at least 6 months
- EMG support of anterior horn cell damage in at least two regions
- exclusion of other pathology by appropriate investigations (see below)
- opinion of two experienced neurologists

Differential diagnosis:

Condition	Comment
Spinal cord pathology, especially cervical myelopathy	May coexist with MND. Consider MRI if appropriate
Multiple CVA	Pure motor syndrome unlikely, consider imaging
Inclusion body myositis	Preferential involvement of quadriceps and finger flexors. May require muscle biopsy
Kennedy's disease (X-linked bulbar and spinal muscular atrophy)	LMN syndrome affecting males only Family history and/or features of androgen resistance (gynaecomastia, testicular atrophy, etc). Diagnosis by detection of trinucleotide repeat expansion in androgen receptor gene
MFMN	Patchy weakness, proportionally greater than wasting. Characteristic immunological and electrophysiological findings. Consider trial of intravenous Ig
Chronic inflammatory demyelinating neuropathy	Symmetrical signs, often sensory symptoms. Raised CSF protein and prolonged nerve conduction studies. Consider steroids and other immunomodulatory treatments
Other rare CNS degenerations:	
Adult onset spinal muscular atrophy	Isolated, usually symmetrical LMN syndrome, slowly progressive
Progressive supranuclear palsy	Vertical gaze palsy, early falls, extrapyramidal features present
Multisystem atrophy	Complex presentation, amyotrophy rare
Cortico-basal degeneration	Presents with features of basal ganglia and cerebral cortex dysfunction, amyotrophy occasionally seen
Machado-Joseph disease (spinocerebellar atrophy type 3)	Complex multisystem presentation overlaps with MND; autosomal dominant inheritance, trinucleotide repeat expansion in gene linked to chromosome 14q23
Dementia-disinhibition-parkinsonian amyotrophy complex	Mutations found in *tau* gene (microtubule associated protein, chromo some 17q), amyotrophy rare
ALS-parkinsonian-dementia complex of Western Pacific	Geographical isolate; cause unknown

Investigations:

Consider use of:

- neurophysiological tests (seeking evidence of anterior horn cell damage in regions not supplied by the same nerve, root or segment)
- serum creatine kinase (often elevated, but seldom >4 x normal)
- brain and spinal cord MRI
- DNA analysis: SOD1 mutation for MND and Kennedy's disease (expanded trinucleotide repeat in androgen receptor gene)
- anti-GM1 ganglioside antibodies (high titre of IgM suggests MFMN)
- Muscle biopsy

ALS = amyotrophic lateral sclerosis; CNS = central nervous system; CSF = cerebrospinal fluid; CVA = cerebrovascular accident; EMG = electromyography; Ig = immunoglobulin; LMN = lower motor neuron; MFMN = multifocal motor neuronopathy; MRI = magnetic resonance imaging; SOD = superoxide dismutase; UMN = upper motor neuron.

Table 3. Contributors to the multiprofessional motor neuron disease (MND) care team approach (community or hospital-based).

- General practitioner and district nurse
- Physiotherapists
- Occupational therapists
- Speech and language therapists
- Dietitians
- Counsellors (for bereavement, family support, etc)
- Specialist nurses
- Palliative care team
- Relevant medical specialties and support staff
- (gastroenterology, respiratory medicine)
- Care coordinators
- Neurologists

Also consider referral to specialist regional or supraregional units with special experience in MND (eg mobility or communication centres, Mary Marlborough Lodge in Oxford for aids, appliances and advice on adaptations).

Table 4. Symptoms and signs suggestive of respiratory muscle involvement in motor neuron disease.

Inspiratory (diaphragm and accessory muscles):
- orthopnoea
- dyspnoea on exertion, after full meal, in swimming pool,
- on bending over
- poor sneeze
- disturbed or restless sleep
- daytime somnolence
- morning headache
- poor appetite
- paradoxical inspiratory abdominal motion

Expiratory muscle weakness:
- poor cough
- loss of abdominal muscle tone

If present consider:
- drugs: are any respiratory suppressants?
- occupational therapy review: is bed adequate?
- physiotherapy review: teaching assisted cough
- further investigation and assessment for respiratory support

community. The Motor Neurone Disease Associations provide practical support, and patients should be given details of the national organisations (the addresses are given at the end of the article). Neurologists and other physicians should play a key role in providing symptom relief, identifying the needs of individuals with MND, and ensuring that appropriate support is available. The key to good management is crisis prevention and awareness of the unique needs of each individual and family.

Imparting the diagnosis

The diagnosis should be communicated in private, with the patient's chosen carer(s) present and with ample time for discussion. Forethought should be given to preparing support, early follow-up and evolution of a management strategy that best maintains the individual's autonomy and quality of life.

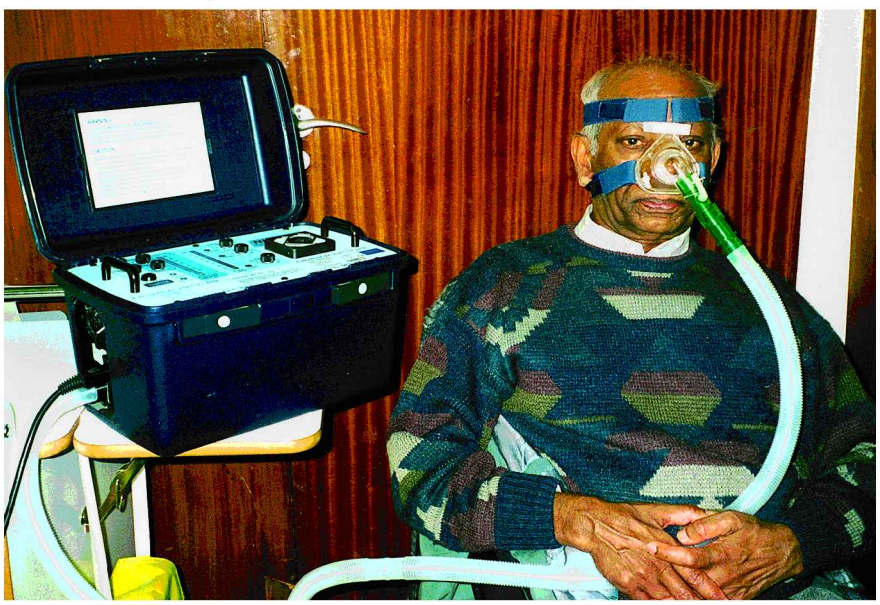
Respiratory care

Death in MND usually results from neuromuscular respiratory failure. Prior to this, chest wall and diaphragmatic weakness can cause significant distress. A history of specific respiratory symptoms, with appropriate signs, should be sought as early indications of respiratory compromise (Table 4). Until recently, respiratory support was rarely provided in the UK but is now available in the form of non-invasive positive pressure ventilation (NIPPV) (Fig 1). The aim should be to provide symptomatic relief, enhancing quality of life rather than prolonging it. Full assessment is needed beforehand (Table 5) as it is not always appropriate (Table 6). Patients and carers should understand that respiratory support is part of palliative care and that the underlying disease will progress. NIPPV avoids tracheostomy, and has been shown to improve survival and respiratory symptoms[8].

Nutritional support

Weight loss and malnutrition are common in MND, even without bulbar weakness. We found that 21% of patients were malnourished, with no difference between bulbar- and limb-onset cases[9]. Possible causes include respiratory failure, depression, infection and anorexia, as well as difficulty in chewing and swallowing. Management involves various disciplines:

Fig 1. Non-invasive positive pressure ventilation (NIPPV) apparatus.



- Speech therapists may assess a patient's swallow, and advise on techniques to ease eating and avoid aspiration.
- A dietitian's review will maximise calorific intake in as easily ingested a form as possible.
- As MND progresses, despite intervention, intake of food and fluid becomes inadequate in many patients. Enteral feeding may then be indicated but, as with ventilation, practical and ethical matters must first be addressed.
- Gastrostomy is more successful, and survival increased, *before* respiratory function deteriorates. It should therefore be considered early, and adequate assistance made available to the patient from carers, family, and community nursing and dietetic staff.

Table 5. Investigation of neuromuscular respiratory function.

Investigation	Comment
Vital capacity: lying and standing	If 100% of predicted, significant respiratory muscle involvement unlikely; >25% fall on lying down suggests diaphragm weakness. Apparently low FVC can be due to poor patient motivation and/or lip seal (as in bulbar weakness)
Maximum inspiratory and expiratory mouth pressures	Problems of motivation and lip seal as per VC
Sniff nasal pressure	Avoids mouthpiece but still needs maximal patient effort
Measurement of transdiaphragmatic pressure after magnetic stimulation of the phrenic nerves	Invasive test requiring placement of oesophageal and gastric catheters, but is only non-volitional test of diaphragm strength
Blood gas	Raised early morning bicarbonate is first sign of hypoventilation, preceding hypercapnia and hypoxia
Polysomnography	Confirms or refutes presence of hypoventila tion-induced sleep disturbance; if not present, look for non-respiratory causes of poor sleep (poor bed, depression). Excludes upper airways obstruction, which may make NIPPV difficult

FVC = forced vital capacity; NIPPV = non-invasive positive pressure ventilation; VC = vital capacity.

Table 6. Indications and contraindications for non-invasive positive pressure ventilation (non-invasive respiratory support) (NIPPV).

Indications:

- Respiratory muscle weakness and symptoms of hypoventilation (poor sleep, daytime somnolence, morning headache, etc) following documented episodes of hypoventilation
- Symptomatic ventilatory failure caused by respiratory muscle weakness

Contraindications:

- Significant bulbar weakness: NIPPV can increase risk of aspiration pneumonia
- Lack of permanent carer at home: as disability increases, help will be needed to apply mask; social services often unable to provide overnight care
- Poor hand function (see above)

These are all relative contraindications, but the implications of using NIPPV in these situations should be discussed with patient, relatives and all health and social care staff

Bulbar dysfunction

To improve communication, speech therapists may recommend aids, ranging from simple pointing boards (lists of words) to computerised speech synthesisers (Fig 2). When speech and swallow are not compromised, excess salivation (sialorrhoea) may be embarrassing and inconvenient. Violent yawning can be a problem, occasionally leading to jaw dislocation. Standard treatments for bulbar spasticity are shown in Table 7.

Limb dysfunction: managing physical disability

The physiotherapist and occupational therapist can give general support and advice on mobility, posture, and appropriate aids and appliances. Specialised services may be employed: regional driving assessment centres, rehabilitation units for provision of environmental control systems (giving control of doors, lighting, etc). Patients often enquire about the place of exercise, but there is no evidence to indicate that any exercise regimen influences disease progression. Cramps often present early in MND, and may be bothersome. Spasticity may compromise mobility, but can in fact aid weak legs to support the body. Fasciculations seldom cause symptoms, and often diminish as disease progresses. Treatment of these symptoms is outlined in Table 7.

Psychological

Depression and anxiety often follow the diagnosis of MND. Both should be treated appropriately, and not viewed as unavoidable consequences of a progressive disease. Emotional lability is usually associated with pseudobulbar

Fig 2. Speech therapist training patient in the use of a speech synthesiser.

palsy and can be treated with antidepressants (Table 7). Carers need support as well: strain within a family or relationship can be made much worse by MND. Individual treatment will vary according to need, from antidepressants to regular respite care, but time should be taken to enquire about the impact of MND on all those whom it touches[10].

Pain in MND is more often commented on by patients than by their doctors. It is often non-specific, but practical measures to reduce it include maintenance of good posture, together with appropriate analgesia.

End of life

Palliative care can be important before the terminal stages of MND. Home care teams and day centres may offer respite care, with a parallel set of therapists and support staff complementing those provided elsewhere. Terminal care often involves alleviating distress from respiratory failure. Patients may experience a frightening sensation of choking due to episodes of laryngospasm. Benzodiazepines and agents to dry secretions may be helpful here, but usually laryngospasm resolves rapidly and spontaneously. Oral, subcutaneous or intravenous morphine may be indicated to relieve dyspnoea, anxiety, pain, hunger or other distress.

Table 7. Treatments used in symptom control.

Symptom	Treatment
Sialorrhoea	Amitriptyline 25–150 mg od Hyoscine patch (1 mg) for 3 days Glycopyrronium bromide 200 µg (via gastrostomy) Unilateral parotid gland radiotherapy
Fasciculations	Carbamazepine titrated from 200 mg bd
Cramps	Quinine sulphate 200 mg on-300 mg bd
Spasticity	Baclofen 5 mg tds initially, increasing as required Tizanidine 2 mg od initially, increasing as required
Emotional lability	Amitriptyline 25–150 mg od SSRI eg citalopram 20 mg od, fluoxetine 20 mg od, paroxetine 20 mg od

SSRI = selective serotonin reuptake inhibitor.

Disease-modifying drugs

Riluzole

Riluzole, which blocks glutamate release, is the only drug that has been shown to increase survival in MND (by about 3 months after 18 months' administration)[11]. However, no convincing effect on functional deterioration was detected in this trial, which did not measure quality of life. With these results, and its relative expense (ca £3,700 per person per year), some UK health authorities will not fund the drug, and it is not licensed in some countries (eg Australia, Canada). Patients usually tolerate riluzole well, though some experience problems with fatigue and nausea. Liver function and blood count should be monitored, and the drug be discontinued if liver function tests exceed five times the upper limit of normal.

Gabapentin

A trial of gabapentin, which possesses antiglutamate properties, showed a trend towards slower progression with treatment[12]. Although the evidence is not strong, it is used in some centres (an off-licence indication) in a dosage that is gradually increased to 400–600 mg tds. The principal side effect is drowsiness.

Vitamin E

Though lacking supportive evidence in humans, vitamin E (in a dose of 800–1,000 mg/day) is often used on the basis that free radical damage may contribute to neuronal death.

Care of other medical conditions

The management of MND should not be to the exclusion of other medical conditions. Specifically, contraception may be required – therapeutic abortion in a young woman with MND is an avoidable tragedy. Easing symptoms from concurrent conditions that are compounded by MND (eg asthma and respiratory failure) may be highly effective.

Conclusions

1 The care of people with MND has been transformed over the last 10–15 years with the development of a multiprofessional approach, although such provision is not universally available in Europe or North America. As with other types of progressive disease, the key to good management is individual care, forward thinking, and preservation of the autonomy and dignity both of the individual affected and of their carers. The voluntary associations have been instrumental in effecting these changes.

2 Good symptomatic relief can be provided for many of the problems experienced by patients. The trend is towards earlier intervention with gastrostomy. The management of respiratory muscle weakness is undergoing rapid change, with some centres routinely assessing patients for non-invasive ventilatory support. Controlled trials examining quality of life after early gastrostomy and following NIPPV are urgently required.

3 Molecular genetics has identified possible pathogenic mechanisms, but the precise aetiology of motor neuron death is not understood. Riluzole, which blocks glutamate release, improves survival at 18 months, but the cost-benefit of this treatment is controversial. Several major trials of neuroprotective agents are under way.

Acknowledgment

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UK patients' associations

1 The Motor Neurone Disease Association (for England, Wales, Northern Ireland, Channel Islands and Isle of Man), David Niven House, PO Box 206, Northampton NN1 2PR. *Tel*: 01604 250 505

2 The Scottish Motor Neurone Disease Association, 76 Firhill Road, Glasgow G20 7BA. *Tel*: 0141 945 1077

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