

THE MANAGEMENT OF MOTOR NEURONE DISEASE

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The management of motor neurone disease (MND) has evolved rapidly over the last two decades. Although still incurable, MND is not untreatable. From an attitude of nihilism, treatments and interventions that prolong survival have been developed. These treatments do not, however, arrest progression or reverse weakness. They raise difficult practical and ethical questions about quality of life, choice, and end of life decisions.

Coordinated multidisciplinary care is the cornerstone of management and evidence supporting this approach, and for symptomatic treatment, is growing.¹⁻³ Hospital based, community rehabilitation teams and palliative care teams can work effectively together, shifting emphasis and changing roles as the needs of the individuals affected by MND evolve. In the UK, MND care centres and regional networks of multidisciplinary teams are being established. Similar networks of MND centres exist in many other European countries and in North America.

Here, we review current practice in relation to diagnosis, genetic counselling, the relief of common symptoms, multidisciplinary care, the place of gastrostomy and assisted ventilation, the use of riluzole, and end of life issues.

TERMINOLOGY

- ▶ Motor neurone disease (MND) is a synonym for amyotrophic lateral sclerosis (ALS).
- ▶ MND comprises several syndromes (classical or Charcot ALS; progressive bulbar palsy—PBP; progressive muscular atrophy—PMA).
- ▶ With the exception of primary lateral sclerosis (PLS) all these share the characteristic pathology of MND. The same applies to the “flail arm” and “flail leg” syndromes (table 1).
- ▶ MND is used throughout this article, except in relation to the El Escorial criteria.

DIAGNOSIS: MAKING IT AND BREAKING IT

The average delay from onset of symptoms to diagnosis is about 14 months, about one third of expected survival. Occasionally, survival following diagnosis may be less than six months. The patient may already suspect the diagnosis and may have visited internet sites or have seen television programmes about people with MND choking to death or demanding the right to assisted suicide. Nevertheless, uncertainty is generally worse than knowing the diagnosis. A diagnosis is usually required before care can be organised.

People with suspected MND should be “fast-tracked” through the health system to avoid frustrating delays. When the patient is seen for the first time, the diagnosis may be obvious. This poses a dilemma. Should the patient be told, or should one wait until the investigations have been completed? If the individual knows or suspects the diagnosis, it may be best to discuss the possibility of MND, outlining how and when the uncertainty will be resolved.

The next step is to exclude other diagnoses (table 2) including rare “MND mimic” syndromes (table 3).

The El Escorial criteria⁴ (box 1) were designed as research diagnostic criteria for clinical trials. Although the criteria strive to codify the process of clinical decision making, patients do not appreciate a diagnosis of “possible” or “probable” MND. The El Escorial categories of possible and probable ALS (MND) are highly predictive of necropsy proven MND.⁵ Thus clinicians can be confident in the diagnosis providing that all the appropriate tests have been done.

Routine blood tests are required to exclude other conditions. Examination of the spinal fluid is usually unhelpful, although the total protein may be a little raised. The presence of a significantly raised protein or cell count suggests the need for further investigation to exclude an ALS mimic, such as meningeal infiltration with lymphoma, or (in LMN syndromes) a motor variant of chronic inflammatory demyelinating neuropathy (CIDP).

Up to 30% of people in whom MND is diagnosed initially may have other conditions, although in specialist neurological practice the figure is probably about 10%.^{6,7} Conditions most frequently misdiagnosed as MND (table 3) include cervical spondylotic radiculomyelopathy,

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Table 1 Clinical syndromes of MND (ALS—amyotrophic lateral sclerosis) and related disorders (modified from Kato *et al*, 2003*, with permission)

| Syndrome | Main clinical features | Prognosis |
|---|--|--|
| Classical ("Charcot") MND (ALS) | Usually limb (spinal) onset of weakness; bulbar involvement usual; combined UMN and LMN signs; M:F ratio 3:2 | 60–70% of all cases at presentation. Median survival 3–4 years |
| Progressive bulbar palsy (PBP) | Onset with dysarthria followed by progressive speech and swallowing difficulties; limb involvement usually follows within months but may be delayed for several years; M:F ratio 1:1 (PBP relatively more common in older women) | About 20% of all cases at presentation. Median survival 2–3 years |
| Progressive muscular atrophy (PMA) | Almost always limb onset; >50% develop UMN signs; ~85% develop bulbar symptoms eventually; heterogeneous condition but majority are MND; M:F ratio 3–4:1 | About 10% of All cases at presentation. Overlap with 'flail arm' and 'flail leg' syndromes. Median survival ~5 years; more long survivors (>10 years) |
| "Flail arm syndrome"; "man in a barrel syndrome"; progressive amyotrophic diplegia; Bernhard-Vulpian syndrome | A syndrome of predominantly LMN weakness of both arms; UMN signs develop in 50–70%; often slow progression; pathology is that of MND | About 10% of all cases. M:F ratio 9:1; prognosis may be better than in typical ALS; ? syndrome more common in people of African and Asian origin |
| "Flail leg syndrome"; "pseudo-polyneuritic" form of MND Monomelic forms of MND | A syndrome of progressive leg weakness, predominantly LMN Rare MND variant with slowly progressive focal (upper or lower limb UMN and LMN syndrome). Distinct LMN form most common in Asia (monomelic juvenile onset amyotrophy; Hirayama's syndrome). Must be distinguished from multifocal motor neuropathy | 5–10% of all cases. Slow progression; must be differentiated from lumbosacral radiculopathy Juvenile onset form is progressive over months or several years and then stabilises; does not generalise. Pathology unknown |
| Primary lateral sclerosis (PLS) | Clinically progressive pure upper motor neurone syndrome; after 5 years rare to convert to ALS, but may do so | 20 years or more |
| MND-dementia syndrome (MND-D) | Dementia of fronto-temporal type present in ~5% of all cases of MND, but 20–40% of patients have subtle cognitive changes of "frontal" type. MND-D may present first with dementia or with MND progressing to dementia, or with a combination of both. About 50% familial | Usually 2–5 years |

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

*Kato S, Shaw P, Wood-Allum C, *et al*. Amyotrophic lateral sclerosis. Neurodegeneration. In: Dickson DW, ed. *The molecular pathology of dementia and movement disorders*. Basel: ISN Neuropath Press, 2003:350–68.

thoraco-lumbo-sacral disc disease (a slowly progressive conus syndrome with predominantly motor symptoms and signs), multifocal motor neuropathy (MMN), adult onset forms of spinal muscular atrophy, motor forms of hereditary or acquired motor and sensory neuropathy (HMSN type 2), myasthenia gravis, inclusion body myositis (IBM), and Kennedy's disease. Myasthenia gravis can be mistaken for MND, particularly in elderly patients with bulbar symptoms. The Lambert-Eaton syndrome occasionally presents with bulbar and respiratory symptoms. Botulism is generally too acute to be confused with MND.

Sjögren's disease may occasionally mimic MND. Hyperparathyroidism may present with weakness and brisk reflexes. Hypoglycaemia with insulinoma may cause wasting of the hand muscles. Autoimmune hyperthyroidism may present with muscle weakness, wasting, and fasciculation (Basedow's disease). Post-irradiation lumbosacral radiculopathy following treatment for testicular cancer or lymphoma causes a syndrome of progressive weakness of the legs, often without significant sensory changes. Parkinsonism or dementia occur in about 5% of all cases, although subtle degrees of cognitive impairment are present in 30–40% of patients. Lymphoma has been linked to MND, but the association is not convincing. It is unlikely that benign monoclonal gammopathy of unknown significance (MGUS) is causally related to MND. Nevertheless, myeloma can be associated with a predominantly motor neuropathy. Breast cancer may be associated with MND and antineuronal antibodies. It is therefore wise to check carefully for breast lesions in women with MND.

Benign fasciculation is a condition of persistent (although often intermittent and variable) muscle twitching. EMG shows no denervation, and the syndrome does not progress to MND.⁸ Benign fasciculation is often felt as localised repetitive twitching affecting different muscle groups at different times. This is not typical of true fasciculation. Health professionals are particularly prone to this complaint. Localised (true) fasciculations of the calf muscles are common and almost always innocent. Interestingly, people who carry SOD1 gene mutations do not develop denervation until the onset of clinical symptoms, suggesting that the "prodromal" phase of ALS is usually relatively short.⁹ This is in keeping with clinical observations in sporadic MND, in which it is rare for cramps and fasciculations to precede the onset of weakness by more than a year.

Diagnostic difficulties arise with patients who present either with only LMN, or with only UMN signs (tables 2 and 3). Specific diagnoses must be sought before applying the label progressive muscular atrophy (PMA), meaning the LMN variant of MND. Likewise, if the patient has only UMN signs (for example, a slowly progressive spastic paraparesis or quadriparesis) it may be impossible to arrive at a definitive diagnosis, although many possibilities can be excluded. In this situation, an honest explanation of the situation is required, with periodic review. In all instances, clinicians must weigh the balance of probability and decide whether or not the patient has MND, even in the absence of unequivocal UMN and LMN signs.

Once the diagnosis is established, the individual should be told. The key to telling the diagnosis appropriately is

Table 2 Motor neurone disorders (modified from Kato *et al*, 2003, with permission)*Genetically determined forms of motor neuron disorder*

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|--|
| Familial MND (ALS) (see table 1) |
| Brown-Vialetto-Van Laere syndrome (early onset bulbar and spinal ALS with sensorineural deafness) |
| Fazio-Londe syndrome (infantile progressive bulbar palsy) |
| Hexosaminidase deficiency |
| Hereditary spastic paraplegia (many forms, including ALS2, ALS4) |
| Spinal muscular atrophy (SMA) |
| ▶ Proximal childhood and later onset forms of SMA (types 1–4), SMN gene related |
| ▶ Distal SMA (various forms) |
| ▶ Distal SMA with vocal cord involvement (Harper Young syndrome) |
| ▶ Adult onset proximal SMA (unrelated to SMN gene mutations) |
| X linked bulbar and spinal muscular atrophy (Kennedy's disease) |
| Hereditary motor and sensory neuropathy (predominantly motor forms) |
| Multisystem disorders with occasional anterior horn cell involvement (e.g. SCA3) |
| Algrove syndrome |
| <i>Apparently sporadic (idiopathic) forms of motor neuron disorder</i> |
| Sporadic MND (progressive bulbar palsy; classical limb onset MND/ALS; progressive spinal muscular atrophy) |
| Primary lateral sclerosis |
| Distal sporadic focal spinal muscular atrophy ("Hirayama syndrome") |
| Atypical juvenile onset MND in South India ("Madras" form of MND) |
| Western Pacific and other similar forms of MND/ALS (Guam, Kii peninsula, New Guinea) |
| Guadeloupe PSP-dementia-MND/ALS syndrome |
| MND with frontotemporal dementia (MND-dementia syndrome; Pick's disease with MND) |
| Multiple system atrophy |
| Progressive supranuclear palsy |
| Corticobasal ganglionic degeneration |
| <i>Acquired forms of motor neuron disorder</i> |
| HTLV-1 associated myelopathy (HAM) |
| HIV-associated MND syndrome |
| Creutzfeldt-Jacob disease (amyotrophic forms) |
| Multifocal motor neuropathy |
| Acute poliomyelitis |
| Lead, mercury toxicity |
| Neuroleptichirism (caused by <i>Lathyrus sativa</i> , containing β -oxalyl-L-aminoacid, BOAA) |
| Konzo (due to toxic cyanogenic cassava) |
| Radiation (e.g. cervical and lumbosacral radiculopathy) |
| Post-polio progressive muscular atrophy syndrome |
| Autoimmune disorders (e.g. Sjögren's disease) |
| Endocrinopathy (hyperthyroidism, hyperparathyroidism, hypoglycaemia) |

empathy. That presupposes some understanding of the individual, his or her family, friends, and social context. The experience of being told the diagnosis of MND often shapes subsequent relationships with doctors and other health care professionals. The diagnosis should be given in privacy, by a neurologist who is experienced in caring for people with MND. Planning is needed to ensure that the spouse or another appropriate person is present, that all test results are available, and that pertinent family, social, and emotional factors have been considered. Some MND care teams have a nurse specialist or team coordinator present. An honest, sensitive, and frank (but not brutal) explanation of the diagnosis should be given. Information should not be forced upon patients. Some patients do not want "all the facts". The person telling the diagnosis must be alert to cues from the patient and family about how much information to impart, and how to shape the interview. There must be time to answer questions, to provide information about the disease and support systems, and to deal with the emotional impact of the bad news. It is also important to explain to the patient that the various forms of MND have different clinical

trajectories. A second opinion should be offered. It is important to provide telephone numbers (and email contacts if relevant) for the team coordinator, and for the appropriate patient support group.

It is important to agree a provisional plan of action. This will usually include contact with the voluntary association, referral to relevant therapists, and a further appointment with the same neurologist within four weeks of the diagnosis, often sooner. It is important that the patient and the family feel supported during the difficult period of coming to terms with the diagnosis and its implications. The options for treatment (for example, riluzole) can be outlined, and the need for assessments by the physiotherapist, occupational therapist, speech and language therapist, dietician, and by a psychological support team, discussed. In our view, counselling should be offered to all patients and to carers. Primary care physicians should be fully briefed and have a key role in coordinating day to day care. Patients find copies of clinic letters helpful in dealing with the many agencies and health professionals that become involved in their care.

GENETICS AND GENETIC COUNSELLING

Five to 10% of people with MND have a familial form of the disease (table 4), usually with autosomal dominant inheritance. Dementia, or MND with dementia, occurs in some families, so a family history of dementia should be sought in patients with familial MND. This may be a frontotemporal dementia and may therefore manifest as personality change, either withdrawal and apathy, or disinhibition (see below).

About 20% of patients with familial MND have a mutation in the gene for copper/zinc superoxide dismutase, SOD1. The issue is complicated by the fact that about 3% of patients with apparently sporadic MND also have SOD1 gene mutations. These are usually low penetrance variants that have not caused known disease in previous generations rather than new mutations. More than 100 SOD1 mutations are known, most of them point missense mutations,^{10 11} but the mechanism by which they cause ALS is unknown.^{12 13}

The principles of genetic counselling and predictive testing for Huntington's disease¹⁰ have been applied to familial MND, and genetic testing should not be carried out without prior counselling. SOD1 gene analysis provides an option for predictive testing in those with a relative known to have an SOD1 mutation. This is complicated by the weak or variable penetrance associated with some mutations, so that identification of a mutation in an unaffected individual does not imply that ALS is inevitable. On the other hand, some mutations are known to be highly penetrant, with a predictable phenotype. One mutation (the D90A mutation) behaves as a recessive trait in most families, but as a dominant trait in others. Genetic counselling therefore must take into account the nature of the mutation and the pedigree. Genetic testing of relatives of people with MND should only be done if the patient has a SOD1 mutation. Otherwise a negative result is meaningless because 80% of individuals with familial MND and 98% of all people with MND do not have SOD1 mutations.

We do not advocate screening for SOD1 gene mutations in people with sporadic MND. A positive result is difficult to interpret in view of the variations in penetrance and phenotype alluded to above and yet would have implications for relatives. We do not consider that SOD1 gene testing is a useful diagnostic test in early onset or atypical sporadic cases for similar reasons. Testing for the D90A mutation may,

Table 3 "MND mimic syndromes": the main differential diagnoses of MND (modified from Kato *et al*, 2003, with permission)

| Final diagnosis | Characteristic features | Distinguishing diagnostic features and investigations |
|---|---|--|
| Cerebral lesions | Focal motor cortex lesions very rarely mimic MND, but frontal lesions with co-existent cervical or lumbosacral root damage may cause confusion | MRI/CT; no EMG evidence of widespread chronic partial denervation (CPD) in limbs |
| Skull base lesions | Lower cranial nerve signs (bulbar symptoms and signs; wasting of tongue, often asymmetrical); seldom significant long tract signs unless foramen magnum involved in addition | MRI; CT with bone windows; no EMG evidence of CPD in limbs |
| Cervical spondylotic myelopathy | Progressive limb weakness, but often stabilises, or may be variably progressive; asymmetrical onset; combined UMN and LMN signs in arm(s); spastic paraparesis; occasionally fasciculations in arms | Pain in root distribution, but pain may not be severe and may resolve quickly; often progression followed by clinical stabilisation; no bulbar involvement; MRI evidence of spinal cord and root compression; evidence of brachial (localised to 1 or 2 segments) CPD on EMG (<i>but</i> patients may have co-existent lumbosacral motor radiculopathy with lower limb CPD) |
| Other cervical myelopathies | Progressive weakness; foramen magnum lesions and high cervical cord lesions may be associated with focal (C8/T1) wasting; syringomyelia usually associated with LMN signs and dissociated sensory loss | Usually involvement of cerebellar and/or sensory pathways; MRI of head and cervical spine reveal pathology |
| <ul style="list-style-type: none"> ▶ Foramen magnum lesions (e.g. Arnold-Chiari malformations; meningioma) ▶ Intrinsic and extrinsic tumours ▶ Syringomyelia | Progressive mixed UMN and LMN syndrome | Usually significant sensory symptoms if not signs; bladder involvement; MRI thoracic and lumbosacral region |
| Conus lesions and lumbosacral radiculopathy; spinal dural fistula | Progressive weakness; bulbar symptoms; sometimes respiratory muscle weakness | Characteristic pattern of weakness and wasting (deep fibres of finger flexors, quadriceps femoris); EMG evidence of myopathy; muscle biopsy definitive test (rimmed vacuoles) |
| Inclusion body myositis (IBM) | | Conduction block on nerve conduction studies (NCS); weakness often out of proportion to wasting; positive anti-ganglioside (GM1) antibodies in ~70%; improvement with intravenous immunoglobulin (IVIg) in ~70% |
| Multifocal motor neuropathy (MMN) | Focal asymmetrical onset, often upper limb; pure LMN syndrome; may stabilise for months or years; M:F 4:1 | Anti-acetylcholine or anti-MuSK antibodies; EMG (repetitive stimulation, single fibre EMG) |
| Myasthenia gravis | Bulbar involvement usually (not always) associated with fatigability, diplopia, ptosis; no wasting; no UMN signs | EMG shows fasciculations without denervation; CPK normal |
| Benign fasciculation syndrome | Benign fasciculations common in calf muscles; fasciculations elsewhere often felt rather than seen and described as localised twitching lasting few seconds; no weakness; patients often health professionals or relatives of people with MND | |
| Kennedy's disease (x linked bulbar and spinal muscular atrophy) | Males symptomatic; slowly progressive bulbar and limb weakness | Family history; fasciculations of facial muscles; gynaecomastia; proximal symmetrical weakness in addition to foot drop; mild sensory neuropathy on NCS; positive CAG repeat mutation in exon 1 of androgen receptor gene |

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however, be useful in patients who present with slowly progressive MND (table 5).

Genetic counselling should be offered for all with a family history of MND, although the specificity of advice that can be offered will depend on the nature of the pedigree. At least eight other definite or probable chromosomal loci for MND and related disorders are known (table 4). Genetic counselling is also possible, and important in Kennedy's syndrome (x linked bulbospinal neuronopathy).

MANAGING MND: THE MULTIPROFESSIONAL OR MULTIDISCIPLINARY TEAM

People affected by MND appreciate and indeed demand a coordinated team approach to care (MND Association Standards of Care: <http://www.mndassociation.org>). After telling the diagnosis, it is helpful to refer the patient to such a team, but equally important is close liaison with the primary care team. The family practitioner should be involved from the outset. For example, referrals to community services

Box 1: Summary of revised El Escorial research diagnostic criteria for ALS⁴ (modified from Kato *et al*, 2003, with permission)

Definite ALS

- ▶ UMN signs and LMN signs in three regions

Probable ALS

- ▶ UMN signs and LMN signs in two regions with at least some UMN signs rostral to LMN signs

Probable ALS: laboratory supported

- ▶ UMN signs in 1 or more regions *and* LMN signs defined by EMG in at least two regions

Possible ALS

- ▶ UMN signs and LMN signs in one region (together), or
- ▶ UMN signs in two or more regions
- ▶ UMN and LMN signs in two regions with *no* UMN signs rostral to LMN signs

UMN signs: clonus, Babinski sign, absent abdominal skin reflexes, hypertonia, loss of dexterity.

LMN signs: atrophy, weakness. If only fasciculation: search with EMG for active denervation.

Regions reflect neuronal pools: bulbar, cervical, thoracic and lumbosacral.

and local palliative care teams are often initiated by the general practitioner, and in the UK National Health Service the day to day management of symptoms depends on the general practitioner. General practitioners are familiar with palliative and end of life care in cancer, and the same principles apply to MND. Furthermore, drug prescriptions and blood tests (for example, for monitoring of liver function tests with riluzole) are more conveniently arranged from the local primary care centre than from hospital. Ideally, all care would be provided in, or close to, the patient's home, but resources do not yet allow that in most countries. Lip service is paid to "seamless" services. As yet these do not exist in the UK. The important point is to identify the "seams" and overcome fragmentation by good team work and coordination.

The forthcoming UK National Service Framework on long term conditions is likely to establish a coordinated team approach as a standard of care for complex progressive disorders such as MND. One of the major difficulties faced by people affected by MND is the fragmentation of services between hospital and community. The team described here represents one possible model, but others are valid, and it is not essential that all team members be in one location. To be effective, the team needs excellent channels of communication, and a coherent philosophy of care. The ideal is to provide a single point of contact through which all the care needs of the individual can be channelled. The coordinator role may be rotated to ease the burden.

The main roles of the various contributors to the team are self evident. The main role of the neurologist is to make and tell the diagnosis, to monitor symptoms and advise on symptom control, and to discuss interventions such as gastrostomy and ventilation. It is, however, vital that each team member is aware of all the issues that affect each patient. Thus regular team meetings, with team "de-briefing sessions" following clinics, are essential. There is, correctly, overlap of roles and collaboration within the team, and also

Box 2: Essential and optional diagnostic tests

Essential investigations

- ▶ Full blood count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP)
- ▶ Biochemical screen (liver function tests, electrolytes, calcium, glucose, creatinine)
- ▶ Creatine kinase
- ▶ Thyroid function tests
- ▶ Autoantibody screen
- ▶ Chest x ray
- ▶ Electromyogram (EMG) and nerve conduction studies

Additional investigations, depending on clinical features

- ▶ Magnetic resonance imaging (MRI) (region depending on symptoms and signs)*
- ▶ Anti-neuronal antibodies
- ▶ Anti-ganglioside (GM₁) antibodies
- ▶ Anti-acetylcholine receptor antibodies/anti-MuSK antibodies
- ▶ Tumour markers
- ▶ Mammography
- ▶ Blood and/or urine analysis for toxins (lead; manganese)
- ▶ Plasma protein electrophoresis
- ▶ White cell enzymes (hexosaminidase deficiency)
- ▶ Very long chain fatty acids (adrenomyeloneuropathy)
- ▶ Cerebrospinal fluid (CSF) analysis (protein, cells, glucose, oligoclonal bands, cytology)
- ▶ DNA analysis: SOD1 gene mutations (familial autosomal dominant MND); androgen receptor mutation (Kennedy's syndrome); spastin and other HSP-related genes (progressive UMN syndromes); neurofilament light chain gene mutations (CMT1E); dynactin gene mutations (familial LMN disorder); SMN gene mutations (late onset SMA); hexosaminidase gene mutations in juvenile or early onset MND
- ▶ Muscle biopsy

*Some would consider MRI as mandatory

between hospital based and community based health providers. For example, the assessment and provision of aids and appliances requires that physiotherapists, occupational therapists, rehabilitation units, and orthotics experts work together. The provision of communication aids (see below) and environmental control systems requires close cooperation between all members of the team and the rehabilitation services responsible for assessing the needs of people with MND who require assistive technology.

The emphasis of care should be on autonomy and choice. People with MND must be able to make informed decisions about interventions such as percutaneous endoscopic gastrostomy (PEG), radiologically inserted gastrostomy (RIG), assisted ventilation, and terminal care, and this requires detailed discussion to weigh the options. Advance directives are important and were used by 97% of patients in a survey of care carried out in the USA.¹⁴ The proportion of patients completing advance directives is probably much lower in Europe, but is likely to grow.

The multiprofessional approach offers people with MND the best hope of maintaining quality of life in the face of deteriorating strength and function. The challenge for neurologists is to secure resources from funding agencies to provide truly multiprofessional teams, and with other professionals to develop new concepts in "patient centred care".

Box 3: Key steps in telling the diagnosis

- ▶ Check the patient's background
- ▶ Ascertain what he/she knows already
- ▶ Ensure that you have all the relevant facts to hand—results, opinions, case notes!
- ▶ Arrange the interview to suit the patient and key family member(s)
- ▶ Ask if the nurse specialist/team coordinator can be present
- ▶ Ensure privacy and comfort and establish rapport
- ▶ Be sympathetic but not sentimental
- ▶ Use the correct terms (that is, MND—not “wear and tear of the motor nerves”)
- ▶ Stop, look and listen: watch for clues (facial expression; body language) as to what to say, how much to say, when to stop, when to invite questions.
- ▶ Explain the nature of the condition; offer written information (this could be from the voluntary association/support group)
- ▶ Be cautious about predictions of prognosis but give the facts, bearing in mind clinical variants and uncertainties about prognosis in individuals
- ▶ Outline what can be done. Discuss pros and cons of riluzole, relevant interventions (depending on current symptoms), patient support groups, information (including internet sites), research
- ▶ Agree on a plan for follow up and support
- ▶ Send a summary of the interview to the patient and communicate promptly with primary care physician, others involved in care, the patient

It is our practice to refer patients early (sometimes at the time of diagnosis) to a local palliative care team. In our experience, this can be explained as a means to provide the best care, and the patient can be reassured that palliative care is not the same as terminal care. Likewise, an offer of psychological support is made to all patients, and to carers. Separate consideration of the needs of carers is essential. Their needs are too often overlooked.

DRUG TREATMENT: RILUZOLE

Riluzole is a benzothiazole derivative with complex effects on glutamate neurotransmission including inhibition of pre-synaptic glutamate release.^{15–17}

The first placebo controlled trial of riluzole in MND (ALS) included 155 patients who were randomised to take either riluzole (100 mg) or placebo over 21 months.¹⁸ Patients were stratified according to bulbar or limb onset. The primary outcome measure was survival. Riluzole significantly reduced the risk of death at 12 and 21 months. Deterioration in muscle strength was slower in patients receiving riluzole compared to placebo.

In order to establish the efficacy of the 100 mg dose, and to investigate a dose effect, 959 ALS patients from seven countries were randomised to placebo, or to riluzole 50 mg, 100 mg, or 200 mg daily.¹⁹ The primary outcome measure was tracheostomy-free survival. Patients were stratified according to bulbar or limb onset. A variety of functional measures were studied including muscle strength and vital capacity, but quality of life was not assessed.

The outcome of this study was a trend towards increased survival with riluzole at 18 months, the end of the double blind phase of the study. There was a significant improve-

ment in survival at one year. The difference in survival and/or tracheostomy between placebo and riluzole 100 mg was 6.4% at 18 months. The gain in survival with riluzole was about three months, but as the Kaplan-Meier survival plot did not reach the median at 18 months, this can only be a rough estimate. There was a clear dose effect. Riluzole was safe, with a low incidence of adverse effects requiring drug withdrawal.

Using the Cox proportional hazards model to adjust for slight differences in known prognostic factors between treatment groups there was a relative risk of death for riluzole versus placebo of 0.65 (95% confidence interval (CI) 0.50 to 0.85) at 18 months. Differences in survival at 18 months between placebo and riluzole 100 mg and 200 mg daily were highly significant after adjustment for prognostic factors.

A third trial did not show a positive effect on survival. This trial included patients who were excluded from the previously mentioned trials, and who were generally more severely affected.²⁰ A meta-analysis by the Cochrane collaboration²¹ concluded that riluzole has a modest effect on survival in MND (fig 1).

Thus there is strong evidence that riluzole treatment at 100 mg daily is associated with a small increase in survival. The increase in life expectancy lies between 2–4 months (at 18 months). It is uncertain whether there is any further gain across the whole duration of the disease since there are insufficient long term data on survival with placebo versus riluzole. Long term projections of gain in life expectancy rely on extrapolation modelling and are of uncertain validity.

Is riluzole cost effective? The analysis performed for the National Institute for Clinical Excellence (NICE) concluded that the base case incremental cost effectiveness ratio (ICER) gave a cost per life year of £39 000 and a cost per quality adjusted life year (QALY) of £58 000.²² The most optimistic ICER (cost per QALY) was £20 000. NICE estimated that the additional cost of making riluzole available to all individuals with ALS in England and Wales would be about £5 million per annum. This is a modest sum in comparison with the cost of new drugs for other serious disorders which affect fewer people.

Neurologists often question whether riluzole is clinically useful, since we have no data on its impact on quality of life. Riviere *et al.*²³ in a post-hoc analysis of the data from the trials, found evidence that its effect is evident in the less severely affected stages of the disease, not just at the end stage. Quality of life for people with MND depends on psychological and “existential” factors rather than on strength and physical function.²⁴ A postal survey of 80 European MND specialists found overwhelming support for the use of riluzole in MND, although most felt that the major benefit was in providing hope.

The UK NICE guidelines restrict prescription of riluzole to patients with probable or definite ALS because those criteria were used in the key trials. Pathological studies unequivocally show that PMA falls within the rubric of MND/ALS.²⁵ In our view, there is no justice in excluding patients with a lower motor neurone phenotype when it is clear that they have MND (ALS).

OTHER CLINICAL TRIALS

Clinical trials in MND¹⁷ have included many agents that might, on theoretical grounds, modify disease progression:

Table 4 Genetics of MND (ALS—amyotrophic lateral sclerosis) (modified from Kato *et al*, 2003, with permission)

| Type of familial ALS and pattern of inheritance | Chromosomal linkage | Gene/protein |
|---|---|---|
| 1. Autosomal dominant familial ALS | 21q22.1–22.2 (ALS1) Over 100 mutations in SOD1 gene, mostly missense mutations, some nonsense mutations leading to truncated protein | Cu/Zn superoxide dismutase 1 (SOD1) |
| 2. Autosomal dominant juvenile ALS | 9q34 (ALS4) Slowly progressive childhood or adolescent onset UMN and LMN syndrome | Unknown |
| 3. Autosomal dominant familial ALS with frontotemporal dementia | 9q21–q22 (ALS-FTD) Several families with ALS, ALS plus dementia, or dementia alone. Dementia is of frontotemporal type | Unknown |
| 4. X linked dominant familial ALS | X _{centromere} (ALSX) | Unknown |
| 5. Autosomal recessive juvenile familial ALS | 2q33–2q35 (ALS2) Several families slowly progressive spastic quadriplegia. Some LMN signs in one family. Pathology unknown | ALS2/Alsin Alsin is a guanine exchange factor (GEF) and is implicated in signal transduction and a variety of other cellular processes |
| 6. Autosomal recessive juvenile familial ALS | 15q15–15q22 (ALS5) | Unknown |
| 7. Autosomal dominant familial ALS | 18q21 (ALS6) | Unknown |
| 8. Autosomal dominant familial ALS | 16q12; variable penetrance. 4 families known. Typical ALS, and ALS with dementia | Unknown |
| 9. Autosomal dominant familial ALS | Unknown (ALS3) (~80% of families) | Unknown |
| 10. Autosomal Recessive Fazio-Londe disease (pontobulbar palsy of childhood without deafness) | Unknown | Unknown |
| 11. Autosomal recessive Brown-Vialetto-Van Laere syndrome (pontobulbar palsy of childhood with sensori-neural deafness) | Unknown Possibly same as Madras phenotype MND | Unknown |
| 12. Autosomal dominant familial amyotrophy with frontotemporal dementia, and parkinsonism | 17q21–17q22 Many phenotypes, mainly FTD, parkinsonism and a few associated with MND | Tau gene/protein |

total lymphoid irradiation, immunoglobulin, electrical stimulation, lamotrigine, topiramate, selegiline, riluzole, acetylcysteine, creatine, vitamin E, verapamil, nimodipine, 3,4-diaminopyridine, ciliary neurotrophic factor, insulin-like

growth factor I, subcutaneous and intrathecal brain derived neurotrophic factor, gabapentin, superoxide dismutase 1, pimozone, methylcobalamin, procysteine, and xaliproden. Sadly, all have failed to modify disease progression. Current

Table 5 Some examples of genotype/phenotype correlations in MND associated with specific SOD1 gene mutations

| Mutation | Inheritance | Penetrance in affected families | Distribution, phenotype | Survival from onset of symptoms |
|--|---|---|--|-------------------------------------|
| Alanine to valine, exon 1, codon 4 (A4V) | Autosomal dominant | Complete | North America. Rapidly progressive mainly LMN syndrome, limb or bulbar onset | <2 years |
| Aspartate to alanine, exon 4, codon 90 (D90A) | Autosomal recessive (homozygous): "Scandinavian recessive D90A MND/ALS" | Complete | Scandinavia; Russia, France, Germany, North America. Slowly progressive, presenting as spastic paraparesis, evolving into limb and bulbar MND. Bladder and sensory symptoms common | 10–20 years |
| Aspartate to alanine, exon 4, codon 90 (D90A) | Autosomal dominant (heterozygous) | Variable | Belgium, UK, USA, Russia. Variable phenotype | Variable; short or long survival |
| Glutamate to lysine, exon 4, codon 100 (E100K) | Autosomal dominant | Variable | Afro-American, German families; variable phenotype | >10 years |
| Isoleucine to threonine, exon 4, codon 113 (I113T) | Autosomal dominant | Very variable; apparently sporadic cases with I113T mutation not uncommon | North America, Scotland. Variable phenotype | Variable; short or long (>10 years) |

Box 4. The team approach to the care of people with MND

Main contributors to the (extended) team

- ▶ Care coordinator
- ▶ Home carer(s)—usually spouse
- ▶ General practitioner and primary care team (e.g. district nurse in UK)
- ▶ Nurse specialist
- ▶ Speech and language therapist
- ▶ Occupational therapist
- ▶ Physiotherapist
- ▶ Dietician
- ▶ Social worker
- ▶ Clinical electrophysiologist
- ▶ Consultant neurologist
- ▶ Consultant in rehabilitation
- ▶ Palliative care team (consultant, nurse specialists, etc)
- ▶ Consultant respiratory physician
- ▶ Respiratory technicians
- ▶ Interventional radiologist (for radiologically inserted gastrostomy—RIG)
- ▶ Gastroenterologist (for percutaneous endoscopic gastrostomy—PEG)
- ▶ Psychology support team (counselling and bereavement support; support for carers)
- ▶ Family and child counselling service
- ▶ Neuropsychologist
- ▶ Neuropsychiatrist
- ▶ Voluntary association staff (e.g. Motor Neurone Disease Association)
- ▶ Volunteer helpers

Box 5: Mechanisms of action of riluzole

1. Blockade of presynaptic glutamate release: ? effects on Na⁺ channels; activation of G-protein linked signal transduction
2. NMDA receptor antagonism: Direct, non-competitive receptor blockade
3. Inhibition of glutamate-evoked Ca²⁺ entry: Activation of G-protein mediated signal transduction
4. Prevention of neuronal depolarisation: Inactivation of neuronal Na⁺ channels
5. Inhibition of apoptosis?: Inhibition of stress activated protein kinase (SAPkinase)
6. Inhibition of protein aggregation?: Preliminary evidence that riluzole reduces accumulation of ubiquitinated inclusions in a Huntington’s disease model

trials include pentoxifylline, minocycline, COX-2 inhibitors, and anti-apoptotic agents.

NUTRITION IN MND

Nutritional status and weight loss are predictors of survival.^{19 26 27} In almost all cases, malnutrition is related to decreased calorie intake, although some patients with respiratory difficulties may be hypermetabolic.^{28 29} The prevalence of malnutrition in MND patients is not known exactly, but varies with the stage and manifestations of the disease. We found that 21% of a cross sectional sample of

patients were malnourished, judged by anthropometric measures, whether or not they had significant bulbar involvement.³⁰ A few patients with MND develop weight gain which can be problematic. Such patients are usually those with predominant leg weakness restricting their mobility without restricting calorie intake.³¹

Dysphagia is a complex phenomenon and should be closely monitored. It comprises labial and lingual dysfunction, palatal incompetence, difficulty triggering the swallowing reflex, pharyngeal weakness, reduction in laryngeal elevation, and cricopharyngeal hypertonus. Swallowing safety and efficiency should be regularly evaluated through careful history taking. Observation of the patient eating and drinking is an important part of the assessment. Clinical observation can be supplemented by investigations such as videofluoroscopy or fiberoptic examination. Pulse oximetry can be used to monitor oxygen desaturation during swallowing. Auscultation of the neck may help to detect aspiration, although silent aspiration is common and if this is suspected videofluoroscopy may detect this. ALS severity scales outline the typical pattern of progression,³² which varies greatly. Education of the patient and carer is required to ensure that adequate nutrition is maintained throughout the disease.

Dysphagia is not the only cause of weight loss in MND. People with MND often feel awkward eating in company and

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)
 Comparison: riluzole 100 mg vs placebo
 Outcome: % mortality at 12 months

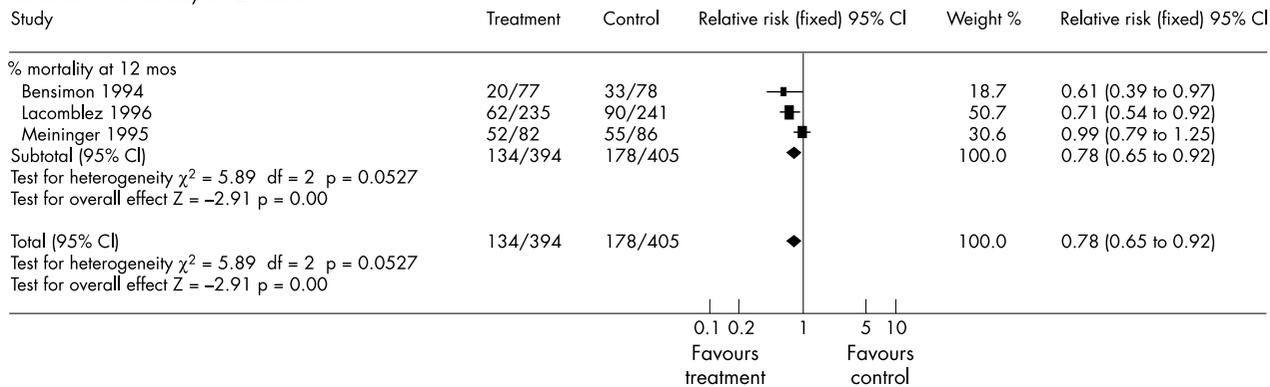


Figure 1 Forest plot resulting from meta-analysis of three randomised, placebo controlled trials of riluzole in MND (ALS). The plot shows the effect on mortality at 12 months. The result favours treatment with a risk of 0.78 (reproduced from Miller *et al*,²¹ with permission).

Box 6: Management of nutrition in MND**The management of nutrition in MND comprises**

- ▶ Assessment and monitoring of dietary intake in relation to the energy, fluid, vitamin and mineral needs of the patient
- ▶ Advice on maintaining a high calorie high protein diet
- ▶ Monitoring of weight and anthropometric measures (>10% weight loss from pre-diagnosis baseline triggers consideration of gastrostomy)
- ▶ Assessment of the need for and timing of percutaneous endoscopic gastrostomy (PEG), radiologically inserted gastrostomy (RIG), or percutaneously inserted gastrostomy (PIG)
- ▶ Advice on gastrostomy feeding, care of feeding tubes, symptoms (for example, constipation)

because they eat slowly, they often fail to finish courses. Arm weakness slows eating and renders patients dependent on others for an adequate food and liquid intake.

Treatment strategies include modifications to the texture and consistency of food (blending food, adding thickeners to drinks), and advising on changes in posture or head position, such as a “chin tuck” manoeuvre (flexing the neck forward on swallowing to protect the airway). Once parenteral feeding is established, oral feeding may be maintained to enhance quality of life as long as there is no risk of aspiration. In patients who cannot take food or drink by mouth, oral hygiene and saliva management are important. Supervision by a speech and language therapist throughout the course of the disease is vitally important, and contributes to decisions on PEG and RIG and end of life care.

Dietary assessment is best carried out by the dietician. Close collaboration with the speech and language therapist is required for the assessment of dysphagia. Weight and height can be used to derive the body mass index ($BMI = \text{weight (kg)}/\text{height (m)}^2$), and skin fold thickness and arm circumference can be used to estimate lean body mass.^{30–33} We now use per cent weight loss as a guide to influence decisions on gastrostomy. Loss of more than 10% of their baseline body weight is an indication to consider gastrostomy.

PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG)

PEG is the standard procedure for maintaining good nutrition in people with MND in whom swallowing is impaired and fluid and nutritional intake inadequate.¹ Existing evidence on the efficacy and risks of PEG is derived from retrospective studies. There are no randomised prospective studies. In our view it would not be ethical to withhold gastrostomy from malnourished patients. We are not, in our opinion, in a situation of equipoise.

What are the risks and benefits of PEG? The benefits include maintenance of good nutrition and prolonged survival.³³ In the study of Mathus-Vliegen *et al*³⁴ on 55 patients with vital capacity (VC) above 1 litre, the procedure related mortality was 1.8% and the 24 hour hospital mortality was 3.6%. These deaths were related to respiratory insufficiency. Major complications occurred in 3.6%, mainly due to infection. The 30 day mortality was 11.5%. Median survival in the PEG group was only 122 days.

In the BDNF phase III study the overall 30 day mortality of PEG was 9.6%, but this was mainly related to the high risk of

Box 7: Summary of assessment for PEG/RIG procedures at the King's MND Care and Research Centre

- ▶ PEG: patients with minor bulbar symptoms and without significant respiratory muscle weakness (that is, VC >50%; SNP >40%; normal overnight oximetry and morning arterial blood pCO_2)
- ▶ RIG: patients with pronounced bulbar symptoms and/or respiratory difficulties

A. Indications for considering PEG or RIG

- ▶ Poor dietary intake and dehydration
- ▶ Patient with bulbar symptoms requests early gastrostomy
- ▶ Significant difficulty swallowing with evidence of aspiration (unsafe swallow)
- ▶ Evidence of failing nutrition (>10% loss of baseline body weight despite nutritional supplements) and/or hydration

B. Relative or absolute contraindications for PEG or RIG

- ▶ Patient unlikely to survive more than 3 months
- ▶ Patient unable to give informed consent
- ▶ Unable to manage feeds; no carer available*

C. Assessment before PEG or RIG

- ▶ Discuss with patient and family in the context of end of life issues to ascertain that the patient and family understand the procedure, its risks, and place within palliative care
- ▶ Assess for evidence of respiratory insufficiency (symptoms; VC >50% predicted; sniff nasal pressure >40 cm water; overnight oximetry shows no significant desaturations; morning blood gases normal)
- ▶ If no evidence of respiratory insufficiency, proceed to PEG or RIG
- ▶ If evidence of respiratory insufficiency, offer and try non-invasive ventilation (NIV) before gastrostomy
- ▶ Delay RIG for 2–4 weeks while patients becomes accustomed to NIV. If swallowing unsafe and/or nutrition and hydration poor, use fine nasogastric tube for feeding/hydration
- ▶ Once NIV established, proceed to RIG
- ▶ Set whole process in the context of palliative and end of life care

SNP, sniff nasal pressure; VC, vital capacity

death in patients with VC < 50%.³⁵ The 30 day mortality of patients with VC > 50% was 0%.

Thus the European and North American experience of PEG is similar. If the VC is greater than 50%, the risk of death in the month after gastrostomy is small. We do not know for certain whether PEG contributes to enhanced quality of life, but there is clinical consensus that it does. There is evidence that PEG prolongs survival (by about eight months), increases BMI, and decreases weight loss.³³

Evidence based practice parameters from North America suggest that PEG should be done before VC falls below 50% predicted.^{1, 33–34} There is no evidence from prospective randomised studies to validate this, nor to indicate what degree of weight loss should trigger PEG. Furthermore, VC is not a good measure for predicting respiratory failure. Patients may develop respiratory failure with a VC as high as 75% predicted.³⁶

Inevitably, many patients who might benefit from PEG decline to have the operation until late in the course of the disease. Should we consider PEG, for example, in a patient who has declined PEG early on in the course of the disease, who now has poor bulbar, limb, and respiratory function,

Table 6 Advantages and disadvantages of PEG, RIG, and NGT (nasogastric tube) hydration and nutrition in MND patients

| Procedure | Advantages | Disadvantages |
|-----------|---|--|
| PEG | Standardised procedure for MND patients; risks and benefits well documented; tubes widely available and standardised | Requires sedation, introduction of endoscope tube, recumbency. Not recommended if VC <50%; requires admission to hospital (4–5 days). Infection may occur around gastrostomy site |
| RIG | Only fine bore NGT tube required (for introduction of air); only local anaesthetic needed; use of the skin level Entristar tube is satisfactory; tolerated well by patients with VC <50%; can be used with NIV | Requires admission to hospital (4 days) but can be performed as day case in patients with good respiratory function and early disease. Local infection may occur |
| NGT | Minor, non-invasive procedure; possible to place in virtually all patients; good for maintaining hydration and avoiding intravenous fluids/feeding in the short term. Should be considered as temporary measure in some patients. We use NGT to improve patients' fitness before RIG* | Nasopharyngeal discomfort, pain or even ulceration if used for more than 6–8 weeks; intrusive and unsightly for active patients; checking for displacement before feeding commences can be a burden for carers; community support varies |

*Some patients delay decision on non-invasive ventilation until VC is <50% predicted or until they develop symptoms of respiratory insufficiency.

who cannot maintain hydration and nutrition, and who is likely to survive only 3–6 months? Our current practice is summarised in box 7.

RADIOLOGICALLY INSERTED GASTROSTOMY (RIG)

RIG offers the advantage over PEG in that it avoids sedation, obviates the need for patients to swallow an endoscope tube, and potentially allows patients to remain upright rather than recumbent.³⁷ All these factors are important in the individual with poor respiratory function. In our experience, RIG can be performed safely in patients with VC below 50% predicted, and in those using non-invasive ventilation. We now perform RIG as the intervention of choice in all MND patients.

The advantages and disadvantages of PEG, RIG, and nasogastric tube hydration and nutrition in MND patients are summarised in table 6.

Box 8: Symptoms and signs of respiratory insufficiency in MND

Symptoms

- ▶ Orthopnoea
- ▶ Dyspnoea on exertion or talking
- ▶ Disturbed night time sleep
- ▶ Excessive daytime sleepiness
- ▶ Difficulty clearing secretions
- ▶ Fatigue
- ▶ Anorexia
- ▶ Depression
- ▶ Poor concentration and/or memory
- ▶ Morning headache
- ▶ Nocturia

Signs

- ▶ Increased respiratory rate
- ▶ Use of accessory muscles
- ▶ Paradoxical movement of abdomen
- ▶ Decreased chest movement
- ▶ Weak cough
- ▶ Sweating
- ▶ Tachycardia
- ▶ Weight loss
- ▶ Confusion
- ▶ Papilloedema (rare)

RIG requires an interventional radiologist experienced in the technique. A nasogastric tube is introduced so that the stomach can be inflated with air. A guide cannula for the feeding tube is introduced through the abdominal wall under local anaesthetic. "T fasteners" are used to secure the stomach wall to the abdominal wall. The sutures are removed 5–7 days after the procedure. The introduction of feeding can commence on return to the ward, with an evening meal on the same day as the procedure. Studies comparing RIG and PEG in patients with VC > 50% are in progress.

MANAGING RESPIRATORY INSUFFICIENCY IN MND

Weakness of respiratory muscles develops as the disease progresses in all patients with MND. Some patients present with respiratory insufficiency.^{38–39} Respiratory failure (defined as arterial or ear lobe $pCO_2 > 6.5$ kPa) may be present in the absence of breathlessness at rest or orthopnoea. Weakness of inspiratory and expiratory muscles is important in symptom production, and respiratory muscle weakness is a significant indicator of survival. The measure of respiratory muscle weakness most often used and widely studied is VC, either slow or forced. VC is the most readily available and practical test for clinic use, and has been widely used as an end point in clinical trials.⁴⁰

As mentioned above, VC has serious limitations as a measure of respiratory muscle function in MND. First, it is

Box 9: Assessments of respiratory function in MND

Essential

- ▶ Checklist of symptoms and signs
- ▶ VC sitting or standing, and lying
- ▶ Morning (ear lobe) blood gases if symptoms present

Desirable

- ▶ VC (lying, and sitting/standing)
- ▶ Sniff nasal pressure (SNP)
- ▶ Nocturnal oxymetry

Optional (research)

- ▶ Detailed ("invasive") studies of respiratory muscle function
- ▶ Polysomnography

Box 10: Provisional European consensus criteria for NIV (European ALS/MND Consortium and European Neuromuscular Centre workshop on non-invasive ventilation in MND, May 2002)

Suggested criteria for non-invasive ventilation (NIV)

Symptoms related to respiratory muscle weakness. At least one of

- ▶ Dyspnoea
- ▶ Orthopnoea
- ▶ Disturbed sleep (not caused by pain)
- ▶ Morning headache
- ▶ Poor concentration
- ▶ Anorexia
- ▶ Excessive daytime sleepiness (ESS >9)

AND

- ▶ Evidence of respiratory muscle weakness (FVC \leq 80% or SNP \leq 40 cm H₂O)

AND

- ▶ Evidence of EITHER:
 - ▶ significant nocturnal desaturation on overnight oximetry

OR

- ▶ morning ear lobe blood gas pCO₂ \geq 6.5 kPa

ESS, Epworth sleepiness scale

relatively insensitive to significant change in respiratory function.^{36–41} Second, patients with bulbar onset disease or pronounced facial weakness cannot perform the test accurately, even using a mask or mouthpiece. Patients with pseudobulbar features often have an apraxia of facial movements and cannot blow effectively despite having good diaphragm function. Third, although VC is a prognostic factor for survival¹⁹ there is a relatively weak correlation between VC, respiratory failure, and survival.³⁶

Sniff nasal pressure (SNP) is a good measure of respiratory muscle dysfunction in MND, combining linear decline, sensitivity in mild disease, and feasibility in severe disease.^{36–41, 42} SNP is easy to perform in a clinic setting. More invasive methods of assessing respiratory muscle weakness (for example, sniff trans-diaphragmatic pressure—sniff pdi) are even better predictors of respiratory failure,^{36–43} but are not practical in routine clinic use. Diaphragm electromyography (EMG) has been used to detect early denervation, and this correlates with dyspnoea⁴⁴ but it is invasive and impractical in most centres.

In summary, VC does not enable clinicians accurately to predict the need for assisted ventilation in MND. It is particularly misleading in patients with bulbar symptoms but no tests—standard, experimental, invasive or non-invasive—accurately predict respiratory failure or death in this group. VC is, however, simple to use in the clinic, and our practice is to monitor VC and symptoms that suggest respiratory insufficiency. It is important to remember that dyspnoea may be due to pneumonia or to pulmonary embolism rather than respiratory failure. Prompt treatment of infection is important, as is prevention by vaccination, and avoiding contact with people with colds or influenza. Deep vein thrombosis and pulmonary embolism are relatively common

Box 11: A planned approach to non-invasive ventilation in ALS

- ▶ Monitor respiratory function and symptoms of hypoventilation in all patients (see above)
- ▶ Consider chest infection if sudden deterioration
- ▶ Discuss with the patient and carers the options for respiratory support in a timely but appropriate fashion (that is, before respiratory symptoms occur)
- ▶ Assess the support available at home. A full time carer who is able to assist the patient in setting up and adjusting the ventilator and interface is essential if NIPPV is to succeed. Assess the likely stress on the main carer, and the support that will be required
- ▶ Discuss with the patient and carer the benefits but also the disadvantages of non-invasive positive pressure ventilation (NIPPV)
- ▶ Discuss NIPPV in the wider context of palliative care. We recommend that all patients who opt for NIPPV should be linked into a palliative care team
- ▶ Discuss end-of-life decisions, advanced directives, power of attorney, the withdrawal of NIPPV, and the pros and cons of tracheostomy ventilation
- ▶ Discuss the techniques and familiarise the patient and carer(s) with the equipment and procedures
- ▶ Teach assisted cough; provide insufflator-exsufflator if available
- ▶ Initiate NIPPV, train patients and carer(s) in the use of the masks and settings, and set in place the appropriate support network
- ▶ Periodically monitor effectiveness of ventilation by overnight oximetry and assessment of symptom relief
- ▶ Periodically assess carer strain, and quality of life of patient and carers
- ▶ Agree a plan for withdrawal of NIPPV with appropriate palliative measures (benzodiazepines, opiates)

in MND and should be treated actively, except perhaps in the final stages of the disease.

Surprisingly, some patients who have severe respiratory insufficiency have few or no respiratory symptoms. Other than breathlessness at rest, symptoms and signs associated with respiratory failure are listed in box 8.

It is more common for respiratory failure to present with a mixture of these symptoms than with breathlessness. Even if the sitting or standing VC is > 50% predicted, it is important to measure blood gases and to carry out sleep studies if any of these symptoms are present and cannot be explained in other ways. It is also important to monitor the VC with the patient lying flat. A supine slow VC that is < 25% of sitting or standing VC strongly suggests diaphragm weakness.⁴⁵ Plasma bicarbonate and chloride may be helpful indicators of respiratory failure, but measurement of morning arterial (or ear lobe) blood gases is more useful.

ASSESSING THE NEED FOR VENTILATORY SUPPORT

One of the earliest indications of respiratory insufficiency in MND is sleep disturbance. Increasingly, full sleep studies (polysomnography) are being used to identify patients who may be helped by non-invasive ventilation. Sleep disturbance occurs at a stage when respiratory muscle weakness is not sufficient to cause daytime hypercapnia.^{46–47} Hypoventilation initially occurs in REM sleep when accessory muscles are less active. During REM sleep, ventilation becomes more dependent on the diaphragm, which is disadvantaged by the supine

position. Episodes of hypoventilation occur during sleep with recurrent arousal and disturbed sleep. Spouses are often more aware of this than patients themselves. Patients may attribute the awakenings to urinary problems and complain of nocturia. Initially hypoventilation is associated with oxygen desaturation, but nocturnal hypercapnia develops as the degree of respiratory muscle weakness increases.

Polysomnography is time consuming, requires an overnight hospital stay, and is thus inconvenient and expensive. A practical approach, short of full polysomnography, is nocturnal oxymetry, which can be done at home. It is not yet clear whether nocturnal oximetry is sufficient to predict the need for assisted ventilation. Polysomnography is not as widely available as oximetry, and is used mainly as a research tool. Nevertheless, polysomnography provides a detailed analysis of the relation between sleep phases, respiratory muscle activity, cardiovascular function, and blood gases which is immensely valuable in understanding the pathophysiology of respiratory failure in MND.⁴⁸

In summary, the assessment of respiratory muscle dysfunction in MND might be stratified into tests that can be regarded as essential, desirable, and optional (research).

The practice parameters of the American Academy of Neurology¹ suggest that a VC of < 50% should trigger counselling on non-invasive ventilation (NIV). It will be clear from the preceding discussions, however, that this arbitrary threshold is too low, and that other assessments are extremely important in deciding which patients might benefit from assisted ventilation. At a meeting of the European ALS/MND consortium sponsored by the European Neuromuscular Centre, provisional criteria for initiating NIV were agreed. These were designed to be simple and practical, and requiring no specialised laboratory support (box 10).

Assisted ventilation can be provided in various ways.⁴³⁻⁴⁹ NIV utilises nasal or face masks, and does not require tracheostomy. Although permanent (rather than intermittent) assisted ventilation (PAV) can be delivered using NIV, long term ventilatory support in MND usually requires tracheostomy ventilation.⁵⁰ At present this is used in less than 10% of MND patients in Europe.⁵¹ This figure is higher in some parts of North America⁵⁰ and particularly in Japan where tracheostomy ventilation may be used in nearly a quarter of patients.⁵¹

Ventilation with techniques such as the rocking bed and various forms of negative pressure devices have now been superseded by positive pressure techniques. These include devices that deliver intermittent inspiratory positive pressure (for example, "NIPPV", B & D Electromedical, UK) or bi-level positive pressure devices which deliver different levels of positive pressure in inspiration and expiration (BiPAP). Continuous positive pressure ventilation (CPAP) is not usually appropriate for patients with MND, although occasionally patients with bulbar problems associated with obstructive sleep apnoea benefit from CPAP.

It is important that the ventilator can be programmed with a default rate so that adequate ventilation will be maintained during apnoea or hypoventilation. Most devices can be triggered by the patient to deliver extra breaths. A variety of interfaces are available, including a nasal mask, a full face mask, or nasal cushions. Soreness or ulceration of the nose can be problematic and measures to prevent this are extremely important, particularly in patients who use NIV for prolonged periods.

Non-invasive positive pressure ventilation (NIPPV) has now become a standard procedure in MND/ALS centres in North America,¹ although wide differences in uptake or access exist in Europe⁵¹ and in the UK less than 5% of patients have access to NIPPV.⁵² The latter may be due to concerns by care providers that NIPPV might impair rather than enhance quality of life, or it may reflect lack of resources. As yet no randomised prospective trials on the efficacy and tolerability of NIPPV for MND have been completed. Nevertheless, there is strong evidence that NIPPV can reverse respiratory failure and improve symptoms in neuromuscular and chest wall diseases, and that it prolongs survival in MND.⁵³⁻⁵⁷ NIPPV is also associated with improvements in key aspects of quality of life and cognitive function, but quality of life for carers may deteriorate.⁵⁸⁻⁶⁰

Patients with pronounced bulbar symptoms often have difficulty with NIPPV⁵⁷ but in our experience bulbar features do not prevent successful ventilation. Some bulbar patients have episodes of obstruction related to abnormal function of the vocal cords, and in our experience these patients are difficult to ventilate satisfactorily with NIPPV. NIPPV increases the risk of aspiration in bulbar patients.

The decision to opt for NIPPV requires careful forethought and counselling as described in box 11.^{50 61 62}

COUGH ENHANCEMENT TECHNIQUES

Expiratory muscle weakness leads to difficulty clearing secretions, plugging of bronchi, and increased risk of infection in patients with MND.⁶³⁻⁶⁴ Apart from suction using a portable home suction device, patients and carers should be taught techniques to assist expiratory movement during cough using a manual thrust to the abdomen, and manual insufflation before cough using a bag and mask may be helpful. A mechanical insufflator-exsufflator applies deep insufflation with positive pressure, followed by immediate exsufflation with negative pressure, via a face mask.⁶⁵ As yet there is no evidence that this device improves outcome in MND, but it does increase expiratory flow rates and may come to play a role in maintaining respiratory function and preventing infection in MND patients.

Carbocysteine (up to 1.5 g daily in divided doses) may be helpful in loosening tenacious secretions and adequate hydration is important. A humidifier may be helpful.

TRACHEOSTOMY VENTILATION

Tracheostomy ventilation is, alas, sometimes initiated inadvertently after a patient presents in respiratory failure.^{43 66} This poses difficult ethical and clinical problems, as neither the patient nor the family have had the opportunity and time to make an informed choice about end of life issues.

For elective tracheostomy ventilation, the same principles apply as for NIPPV, but the consequences for long term care are more profound. The attitude of carers must be explored in detail, as tracheostomy ventilation will profoundly affect future quality of life of the carer and the family. Patients may be maintained on tracheostomy ventilation until they become "locked in" and unable to communicate by any means, although the slightest movement may be exploited for communication. Tracheostomy ventilation at home is feasible, but is seldom discussed in the UK. Our practice is to discuss tracheostomy ventilation with all patients, but we do not recommend it. In Japan many more people with MND have

Table 7 Some common symptoms and their treatment in MND

| Symptom | Cause | Treatment |
|---|--|--|
| Cramps | Changes in motor function? | <u>Quinine sulfate 200 mg twice daily</u> Neurone Na ⁺ channel Carbamazepine Phenytoin Magnesium Verapamil |
| Spasticity | Corticospinal tract damage | <u>Baclofen 10–80 mg daily</u> <u>Tizanidine 6–24 mg daily</u> <u>Dantrolene 25–100 mg daily</u> Intrathecal baclofen Memantine 10–60 mg daily Baclofen 10–30 mg daily? |
| Excessive or violent yawning | Corticospinal tract damage? (pseudobulbar syndrome) | |
| Sialorrhoea | Bulbar weakness | Home suction device <u>Atropine 0.25–0.75 mg three times daily (tabs/liquid)</u> Atropine eye drops sublingual Benztropine (tabs/liquid) Benzhexol (tabs) Hyoscine (tabs/transdermal patches) Amitriptyline oral (tabs/liquid) <u>Glycopyrrolate (liquid: sc/im/via PEG)</u> Salivary gland irradiation Transtympanic neurectomy (?) Botox injection to salivary glands (?) Carbocisteine (syrup: 250–750 mg three times daily orally or via gastrostomy) <u>Assisted cough</u> Amitriptyline SSRIs (e.g. citalopram, fluvoxamine) Dextrometorphan plus quinidine (?) Lorazepam (sublingual, oral: 0.5–4 mg) Diazepam suppositories Midazolam (e.g. 2.5 mg stat, 10 mg/24 hours via gastrostomy or syringe driver) |
| Tenacious secretions; weak cough | Bulbar and respiratory muscle weakness | |
| Emotional lability | Pseudobulbar syndrome | |
| Anxiety | Many factors | |
| Respiratory distress | Respiratory muscle weakness | <u>Oral morphine (2.5 mg four times daily initially; doses over 100 mg daily may be appropriate) (in addition to or subcutaneous without NIV)</u> Benzodiazepines (sublingual, oral; as suppositories) Morphine or diamorphine (subcutaneous infusion) Reassurance; avoidance of triggers; sublingual lorazepam? (but spasms usually end within 30–60 seconds) |
| Laryngospasm | Pharyngeal sensitivity | |
| Constipation | Immobility; opiates | Hydration; dietary measures; drug management; laxatives |
| Pain | Dehydration Immobility, stiffness | Comfort (seating, sleeping, night and day care); simple analgesics; NSAIDs; opiates; antidepressants; gabapentin |
| Insomnia | Discomfort, pain, depression; (consider respiratory insufficiency) | Comfort; antidepressants; hypnotics; adequate analgesia |
| Depression | Hopelessness; inability to communicate; frustration | Psychological support and counselling; SSRIs; other antidepressants |

Treatments that most often prove helpful are underlined; experimental or unproven treatments are indicated by a question mark.

tracheostomy ventilation, but no information on quality of life of patients or carers is available from Japan. A Cochrane review of assisted ventilation for MND is in progress.

COMMUNICATION

Verbal communication is impaired in over 80% of our patients with MND over the course of the disease. In people with bulbar onset, dysarthria is usually the earliest symptom, and the patients may become anarthric within a few months. Management of the dysarthria includes advice on strategies to optimise the intelligibility of speech such as reducing the background noise, facing the listener, and slowing the rate of speech. Voice amplifiers may be helpful for those patients with good articulation but a weak voice due to respiratory muscle weakness. Alternatives to speech are often sought as the disease progresses. Writing may be the first solution, but

there are also a wide variety of high and low tech devices to support communication on the market. The Lightwriter from Toby Churchill Ltd is an example of a “type to speech” output device, which is widely used in the UK. As hand function deteriorates the machines can incorporate scanning systems operated by switches. Switches have been designed to exploit the slightest purposeful and reproducible muscle movement. Computers and increasingly sophisticated but “user friendly” software have added to the choices available. Expert advice is required in assessing the most appropriate system for each individual. Technology, however, may not always provide a solution. Alphabet boards and individualised picture communication charts may be preferred. The speech and language therapist has to work closely with the patient, their family and carers to find and continually review the optimal communication support system.

COGNITIVE ABNORMALITIES IN MND

There is now abundant evidence that MND is associated with dementia.^{67–70} MND with dementia (MND-D) is a frontotemporal dementia (FTD) with a characteristic molecular pathology, and there is overlap with FTD lacking motor neurone degeneration. In our experience MND-D is rare, affecting perhaps 5% of our clinic population. Others have suggested that MND-D may be present in about 25% of MND patients.⁷⁰ This may reflect a referral bias. Nevertheless, it is clear that 20–40% of patients with MND show cognitive impairments of frontal type,⁷¹ and that these impairments are rather more common in patients with pronounced bulbar symptoms (that is, the pseudobulbar syndrome) than in MND with mainly limb involvement.⁷² Some patients develop aphasia and some apraxia of speech. There seems to be a spectrum of cognitive impairment encompassing entirely normal cognitive function, barely detectable changes in executive and memory functions, and FTD. The more subtle changes must be recognised as they impact upon care. The spouse or carer of an MND patient will often comment that he or she is “not the same person” mentally, showing subtle changes in character and behaviour. In practice, it is difficult to know whether this is a consequence of the distress and frustration of the disease, or a reflection of cognitive impairment. Our suspicion is that clinically significant cognitive change is common, but often undetected, not least because difficulties in communication so often preclude accurate assessment. Such apparently minor changes in character (“personality”) can complicate or even prejudice the provision of care. Neuropsychological and neuropsychiatric evaluations are helpful in this context.

OTHER ASPECTS OF SYMPTOMATIC TREATMENT

Symptoms in MND may be directly related to the disease (for example, weakness and atrophy, cramps, fasciculations, spasticity, dysphagia, dyspnoea, emotional lability, symptoms related to hypoventilation, drooling of saliva, difficulty clearing thick mucous secretions) or indirectly related (for example, psychological disturbances, sleep disturbances, constipation, pain and discomfort). In fact, these distinctions are somewhat arbitrary. All symptoms need to be treated on their merits when they impair quality of life (table 7). Pain is common when patients lose their normal mobility, and standard drugs for pain relief should be used appropriately, bearing in mind that side effects of non-steroidal anti-inflammatory drugs (NSAIDs) and opiate related drugs can be troublesome. Opiates are probably underused. They are effective in relieving breathlessness and anxiety, and do not necessarily shorten life.⁷³ Care should be taken to use the minimum effective dose, to avoid side effects such as myoclonus, and to manage constipation. Morphine or diamorphine can be used subcutaneously. Ratios for converting oral doses of various opiates to subcutaneous doses of morphine sulfate or to diamorphine are available.⁷⁴ Guidelines providing equivalent doses of morphine and diamorphine that can be given orally, by intramuscular injection or by subcutaneous infusion are available.⁷⁵ The many side effects of opiates should be monitored.⁷⁵ Opiates can be combined with benzodiazepines by mouth, through a gastrostomy, or subcutaneously via a syringe driver. Diamorphine is preferred for injection as it is more soluble than morphine and can be given in a smaller volume.⁷⁴ Parenteral midazolam and diamorphine are used when the

patient decides that NIV should be withdrawn. Phenothiazines are sometimes used in addition to benzodiazepines and opiates to relieve anxiety and distress, but in our experience they are seldom necessary.

The involvement of a pain team is sometimes needed. A degree of depression is common in MND patients but suicide is relatively rare. This may change as more people pursue the possibilities of euthanasia or physician assisted suicide. Depression may be as prevalent in carers as in those with the disease. Support for carers and the family is an important aspect of palliative care. Discussion of sexual activity is often neglected and should be considered. Psychological support for the children of people with MND is also important, although specific expertise in child and family counselling is sometimes difficult to find.

Sialorrhoea is often difficult to control. Radiation of the parotid glands is often effective⁷⁶ but in our experience patients are reluctant to pursue this option. Botulinum toxin injections may be helpful, but in our experience superficial injection over the glands is not effective. Deeper injection into the substance of the parotids may prove to be useful. There is concern in patients with MND that botulinum toxin, even at low doses, will weaken already compromised swallowing and breathing. Randomised trials are needed to study the efficacy and safety of botulinum toxin injections in addition to standard treatments.

It should be added that many patients explore complementary approaches to care. Anecdotally, many complementary treatments appear to be helpful and provide great psychological support. Objective evidence for efficacy is lacking, as in many “standard” treatments.

The practice parameters of the American Academy of Neurology usefully summarises the evidence for symptomatic treatments in MND.¹ A detailed description of symptomatic treatment and other aspects of palliative care will be found in *Palliative care in amyotrophic lateral sclerosis*.⁷⁷

In the last stages of the disease, when it is agreed with the patient and family that further active interventions are not indicated, the use of opiates is helpful in relieving distress, hunger, and dyspnoea. Likewise, if patients opt to cease assisted ventilation, sedation and relief of anxiety can be provided with a combination of opiates and anxiolytics.^{49 74 77}

Understandably, the media often emphasise the most negative images of MND—“choking” (people with MND do not choke to death, in fact), helplessness, and assisted suicide. They also misrepresent modest advances in our understanding of MND as “breakthroughs”, unrealistically raising the hopes and expectations of people affected by MND. Despite this, our experience with MND over the last 10 years, during which we have seen more than 1000 people with the disease, emphasises the fortitude, humour, and dignity of people with this disorder. Quality of life can be good, even when the disease is advanced. The challenge is to match care (be it life prolonging or life shortening) to the ever changing needs of the individual with MND, and his or her family.

The increasing dialogue between researchers, clinicians, and people affected by MND to improve understanding of all these issues is extremely positive. Lacking a treatment that can arrest disease progression, we must focus on even better integration of services, and even greater responsiveness to individual need.

CONCLUSIONS

- ▶ People affected by MND (ALS) are best served by a multiprofessional team approach that is “user centred”. New models of user involvement are being developed. This approach will be embedded within the National Service Framework for long term conditions.
- ▶ In randomised controlled trials, riluzole was associated with improved survival at 12 and 18 months, but the survival gain (estimated at 2–3 months at 18 months) beyond 18 months is unknown. Riluzole is relatively safe and well tolerated.
- ▶ PEG is associated with prolonged survival and improved nutrition, but is hazardous in patients with VC < 50% predicted. RIG may offer advantages over PEG.
- ▶ New evidence suggests that both survival and quality of life is improved by non-invasive positive pressure ventilation (NIPPV) but as yet there are no agreed criteria for initiating NIPPV. Currently 10–20% of patients in Europe have NIPPV but this varies widely in different centres and in different countries.
- ▶ Maintaining communication is central to allowing autonomy.
- ▶ Palliative care encompasses the entire course of MND, not only the final phase. Symptom control is important at all stages. Advance directives are helpful.

Ethical concerns about end of life decisions (for example, withdrawing ventilatory support; physician assisted suicide; euthanasia) are under debate.

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