REVIEW

Motor neurone disease

K Talbot

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Motor neurone disease (MND), or amyotrophic lateral sclerosis (ALS), is a neurodegenerative disorder of unknown aetiology. Progressive motor weakness and bulbar dysfunction lead to premature death, usually from respiratory failure. Confirming the diagnosis may initially be difficult until the full clinical features are manifest. For all forms of the disease there is a significant differential diagnosis to consider, including treatable conditions, and therefore specialist neurological opinion should always be sought. Clear genetic inheritance has been demonstrated in a minority of patients with familial ALS but elucidation of the biological basis of genetic subtypes is also providing important information which may lead to treatments for sporadic forms of the disease. In the absence of curative or disease modifying therapy, management is supportive and requires a multidisciplinary approach. If, as seems likely, complex inherited and environmental factors contribute to the pathogenesis of MND, future treatment may involve a combination of molecular based treatments or restoration of cellular integrity using stem cell grafts.

Neurologists in the 19th century recognised that muscle weakness could be due to primary disorders of muscle or secondary to loss of neuromuscular integrity, as happens when peripheral nerves are cut or when motor neurones degenerate. Furthermore, it was observed that there are forms of motor neurone degeneration which selectively affect upper motor neurones or lower motor neurones. A combination of upper and lower motor neurone dysfunction was named amyotrophic lateral sclerosis (ALS) by Charcot and Joffroy.¹ In the USA, ALS or Lou Gehrig's disease are terms used to describe all forms of the disease, whatever the combination of upper and lower motor neurone involvement. In the UK the umbrella term motor neurone disease (MND) is more common. MND is a disease of middle to late life with a mean age of onset of 58 years.² Although the third commonest neurodegenerative disease after Alzheimer's and Parkinson's diseases, MND is relatively rare, with an apparently uniform incidence of approximately 2/100 000 where adequate epidemiological data exists.^{3,4} Despite its rarity, the disease has attracted a lot of attention, as its devastating course places it at the centre of the ethical debate about end of life decision making and physician assisted suicide.

In addition, there are a large number of diseases of diverse aetiology in which motor neurones are involved, either specifically, or as part of a more diffuse neurodegenerative process. Viral infections, toxic insults, and immune mediated disease can all lead to motor neurone degeneration. In contrast, MND or ALS is a progressive degenerative disease of unknown aetiology. In discussing the differential diagnosis of motor neurone disorders it is useful to consider the different presentations of the condition in terms of the relative involvement of upper and lower motor neurones.

AMYOTROPHIC LATERAL SCLEROSIS ("CHARCOT ALS")

In its typical form with evidence of both spinal and cortical involvement, the diagnosis is usually clear. The combination of asymmetrical weakness and wasting in the limbs associated with clinical evidence of corticospinal tract damage (increased tone, brisk reflexes, extensor plantars) typically comes on insidiously over months and accounts for about 85% of all cases of MND. The disease usually begins either in one limb (foot drop or wasting of the intrinsic hand muscles) or with a combination of bulbar and corticobulbar symptoms (dysphagia, dysarthria, tongue wasting, and a brisk jaw jerk). The latter condition is particularly common in women presenting after the age of 50 and carries a poor prognosis. Despite this apparent focal onset the majority of patients have evidence of more diffuse motor involvement when first examined by a neurologist. When signs are confined to the structures below the neck (that is, there is no tongue wasting or pathologically brisk jaw jerk) then magnetic resonance imaging (MRI) must be performed to exclude spinal cord compression, which can occasionally cause a pure motor syndrome. Clinically detectable sensory involvement should raise the suspicion of an alternative diagnosis such as an inflammatory neuropathy. Diffuse fasciculation as an isolated symptom (often combined in an anxious patient with brisk reflexes) often raises the spectre of ALS but is usually due to benign fasciculations, exacerbated by caffeine, anxiety, and sympathomimetic drugs such as inhalers given for asthma. The extraocular muscles and sphincter function are spared in typical ALS. A small proportion of patients with ALS, approximately 3%–5%, show clinical evidence of dementia with a predilection for abnormalities of executive function. Very rarely this can be the

Correspondence to:
Dr Kevin Talbot,
Department of Clinical
Neurology, Radcliffe
Infirmary, Oxford
OX2 6HE, UK;
kevin.talbot@clneuro.ox.ac.uk

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Abbreviations: ALS, amyotrophic lateral sclerosis; MND, motor neurone disease; MRI, magnetic resonance imaging; SOD-1, superoxide dismutase type 1

presenting or dominant feature and there are rare forms of inherited neurodegenerative disease in which ALS, frontotemporal dementia, or parkinsonism can exist in variable degrees within the same family.³⁻⁶ The significance of this association is that there are likely to be common susceptibility factors shared by a number of forms of inherited and sporadic neurodegenerative diseases.

Over the last decade a number of reports of an ALS-like condition occurring in HIV positive patients have appeared. The condition is distinguished from typical ALS by a younger age of onset, progression over weeks to months, abnormal cell counts in the cerebrospinal fluid, and a response to antiretroviral drugs.^{7,8} The occurrence of an ALS-like syndrome as a paraneoplastic manifestation of cancer remains controversial.⁹ There are more convincing series of patients with lymphoma and ALS, but an aetiological association has not been proved.¹⁰

PURE LOWER MOTOR NEURONE SYNDROMES

A minority of patients (approximately 10%) present without upper motor neurone involvement. In the absence of typical features of ALS it is more difficult to be certain of the diagnosis until upper motor neurone signs such as brisk reflexes or extensor plantars become evident. When the tempo of the disease is the same as for ALS with progression over months then the diagnosis can usually be made firmly. Overall, MND presenting as a pure lower motor neurone syndrome (termed progressive muscular atrophy) is more slowly progressive than full blown ALS. Regional variants where involvement remains confined to the lower or upper limbs respectively, are described.¹¹ Myasthenia gravis presenting with predominant bulbar weakness is occasionally misdiagnosed as ALS. High dose radiotherapy can lead to the appearance of a regional lower motor neurone syndrome up to 20 years after treatment.¹²

It is important to appreciate that there is a group of inherited conditions called spinal muscular atrophies in which a pure lower motor neurone pattern of weakness develops in early life and progresses very slowly.¹³ While these disorders can be inherited as an X-linked, autosomal dominant or recessive trait, it is not uncommon to find apparently sporadic cases with onset in adult life. Such patients are often thought to be suffering from MND leading to an unduly pessimistic prognosis being offered. Specific genetic tests are available for X-linked bulbospinal neuronopathy (Kennedy's disease), which causes a slowly progressive lower motor neurone syndrome, sensory neuropathy, and partial androgen insensitivity leading to gynaecomastia,¹⁴ and the recessive form of proximal spinal muscular atrophy which can occasionally come on in adult life.¹⁵ A slowly progressive pure lower motor neurone syndrome in one limb may be due to an immune mediated condition called multifocal motor neuropathy with conduction block.¹⁶ Typical features are profound weakness with minimal wasting, selective involvement of finger extensors, and the presence of antiganglioside antibodies in about 40%. It is an important condition to consider because it responds well to treatment with intravenous immunoglobulin.¹⁷ Similarly, there is a curious form of sporadic benign focal amyotrophy which presents in males in the second or third decade and is much commoner in Japan and the Indian subcontinent than in Europe.^{18,19} Wasting and weakness appears in one (usually an upper) limb over a period of months to years and then seem to plateau or to be only slowly progressive. In 40% of cases the contralateral limb is affected. The condition is of unknown aetiology. As with spinal muscular atrophy, patients are often initially suspected to have ALS.

Bilateral wasting of the limbs with either an upper or lower limb pattern can be caused by the inflammatory myopathy

Box 1: Potentially treatable causes of apparent MND

Mixed upper and lower motor neurone syndrome

- Compressive myeloradiculopathy.
- HIV infection.

Pure lower motor neurone syndrome

- Multifocal motor neuropathy with conduction block.
- Pure motor chronic inflammatory demyelinating polyneuropathy.
- Toxic neuropathies.
- Myasthenia gravis.

Pure upper motor neurone syndrome

- Cord compression.
- B12 deficiency.

inclusion body myositis. While it is usually possible to distinguish this condition using electrophysiological tests, occasional patients show denervation changes.²⁰ Muscle biopsy can be performed to confirm the diagnosis.

PURE UPPER MOTOR NEURONE SYNDROMES

A small percentage of patients appear never to develop any lower motor neurone signs or at least not until very late in their illness. The term primary lateral sclerosis has been used to describe this condition which is generally considered to be aetiologically related to ALS.²¹ The principal distinguishing features of primary lateral sclerosis are the symmetrical progression of a spastic tetraparesis with pseudobulbar palsy (a brisk jaw jerk, stiff slow tongue, and a characteristic spastic dysarthria in which patients are described as sounding as if they have a hot potato in their mouth), a 3:1 male to female ratio, longer survival than ALS (mean 8.5 years, range 5–15 years), relative preservation of muscle strength and prominent emotional lability, usually without cognitive impairment.^{22,23} It is rare and accounts for about 1% of cases of MND. The differential diagnosis includes other causes of the syndrome of progressive spastic paraparesis such as hereditary spastic paraparesis, primary progressive multiple sclerosis, B12 deficiency and, rarely, structural lesions of the brain, including diffuse small vessel cerebrovascular disease. Electromyography may be useful if clear lower motor neurone involvement can be demonstrated but many patients with primary lateral sclerosis have normal electromyograms throughout their illness. Confusion occasionally arises between this form of MND and progressive supranuclear palsy, a degenerative condition presenting with axial rigidity, falls, loss of vertical gaze and cognitive dysfunction which usually runs a more rapidly progressive course than primary lateral sclerosis.

INVESTIGATION (BOX 2)

There is no specific test for ALS, which remains a clinical diagnosis. Diagnostic criteria exist, primarily for the purpose of standardising entry into clinical trials but the clinical usefulness of these schemes in individual cases where there is diagnostic uncertainty is less clear.²⁴ The main focus of investigation in the context of suspected MND should always be the exclusion of a treatable condition (box 1) and swift resolution of diagnostic uncertainty. It is generally prudent to have a low threshold for MRI to avoid missing spinal cord compression. This is mandatory if clinical signs are restricted to the limbs. Most neurologists perform MRI of the whole neuraxis for a pure upper motor neurone syndrome. High quality diagnostic neurophysiology provides essential support to the diagnosis. It is important to appreciate that electrophysiological tests are confirmatory, not diagnostic, and must be interpreted in the context of the clinical syndrome. In typical MND motor nerve conduction velocity is normal (slow conduction suggests a

Box 2: Investigation of suspected MND**Mixed upper and lower motor neurone (ALS) syndrome**

- Nerve conduction studies and electromyography.
- MRI of the spinal cord (brain).
- Routine blood tests, thyroid function, serum electrophoresis.
- HIV test if appropriate risk factors.

Pure lower motor neurone syndrome

- Genetic tests (if slowly progressive, suggesting spinal muscular atrophy).
- Nerve conduction studies/electromyography for conduction block.
- Routine blood tests, thyroid function, serum electrophoresis.

Pure upper motor neurone syndrome

- MRI of the spinal cord (brain) as appropriate to the level of the neurological signs.
- B12/folate.
- Central motor conduction time (using transcranial magnetic stimulation techniques, not routinely available).
- Lumbar puncture.

neuropathy), sensory studies are normal, and electromyography reveals diffuse fibrillation and fasciculation. There is no consensus on the role of lumbar puncture, which is normal in typical ALS and should therefore be reserved for atypical cases as it introduces a delay in confirmation of the diagnosis. It is suggested that a lumbar puncture should be performed in the following clinical situations: (a) in pure upper motor neurone syndromes (spastic paraparesis) to exclude primary progressive multiple sclerosis, (b) if a paraprotein is present on serum electrophoresis or if there are other reasons to suspect an underlying paraneoplastic syndrome, and (c) in very rapidly progressive motor neurone syndromes, particularly in young patients where remote diagnostic possibilities include porphyria, poisoning, or the possibility of a treatable immunologically mediated neuropathy.

MAKING THE DIAGNOSIS

As indicated in box 3, MND can occasionally present to non-neurologists if the onset of symptoms is sufficiently focal to suggest local pathology. Dysphagia or dysarthria is often referred to ear, nose, and throat surgeons if malignancy is suspected. Similarly, a number of patients see orthopaedic or neurological surgeons if the first symptoms indicate the possibility of nerve root compression or cervical spondylosis. Degenerative changes are common in the age group most at risk of MND and a number of patients will undergo decompressive procedures of the cervical spine before the diagnosis of MND becomes apparent when they continue to deteriorate and develop bulbar signs. Very occasionally patients have relatively isolated weakness of respiratory muscle and may present to chest physicians with respiratory failure or obstructive sleep apnoea. Progressive decline in mobility in elderly patients with multiple comorbidities may mask MND. In this population it is suspected that the condition is underdiagnosed.

The diagnosis of MND should only be imparted to the patient by a doctor who has sufficient experience of the condition to be (a) certain of the diagnosis, (b) able to give an honest and accurate prognosis, and (c) initiate appropriate supportive therapy and contact with paramedical specialists who are familiar with the management of progressive neurological disability. In the majority of cases this will be a neurologist. Ideally the diagnosis should be made in hospital after all investigations have been performed, in an appropriately quiet setting with a close relative and a nurse present.

Box 3: MND presenting to non-neurological specialties**Respiratory**

- Progressive respiratory failure.

Ear, nose, and throat

- Dysphagia.

Orthopaedics/neurosurgery

- Foot drop or other symptoms suggestive of compressive radiculopathy.

Elderly care

- Difficulty walking.

There should be adequate time for full discussion of the implications of a diagnosis of MND. A follow up outpatient visit should be arranged within a few weeks as many questions will not be addressed at the initial conversation.

The prognosis for patients with MND is variable and this must be emphasised at the time of diagnosis. ALS is usually relentlessly progressive and malignant in its behaviour. Approximately 50% of patients in most series are dead 2–3 years after the initial diagnosis.² Most patients fear that death will be by sudden asphyxiation or choking but there is evidence that the majority of people with ALS given adequate palliative care die peacefully at home or in a hospice from respiratory failure and chest infection.²⁵ In contrast, 20% and 5% of patients are alive at five and 10 years respectively. The prognosis is generally worse if the onset of the disease is bulbar and there is early evidence of respiratory muscle compromise. A predominantly lower motor neurone picture is generally more slowly progressive, as is disease which is confined initially to the upper limbs. As mentioned above, patients with primary lateral sclerosis may survive for decades. Therefore most specialist clinics will have experience of patients who survive for many years longer than initially expected. These patients necessarily have complex needs which are often best met by a specialist neurorehabilitation team.

PATHOGENESIS

The aetiology of the vast majority of cases of ALS is unknown. Though the uniform incidence of MND throughout the world has been disputed,²⁶ with the exception of geographical isolates such as on Guam and Guadeloupe, there is remarkably little variation in published studies. This does not immediately favour either an environmental or genetic cause. An apparent increase in incidence in the disorder in the last few decades may be due to improved diagnosis, an aging population, or a genuine increase the frequency of the disease. Specific MNDs are known to be caused by dietary factors in the tropics (konzo in Africa and lathyrism in India).^{27, 28} Numerous theories have implicated environmental poisons such as pesticides and heavy metals, but epidemiological evidence for this as the cause of typical sporadic ALS is lacking. Rare reports of ALS after electrocution probably represent a genuine biological phenomenon,²⁹ but this does not seem to provide an insight into the origin of the vast majority of cases. Autoimmune factors have also been explored in some detail. While there is evidence of factors in patient serum that may damage motor neurones in culture, immunomodulation with steroids, intravenous immunoglobulin or plasma exchange has not been shown to be an effective treatment.³⁰ A viral aetiology is an attractive hypothesis because of the role of an enterovirus in poliomyelitis. Reports of persistent enteroviral RNA in postmortem material from ALS patients continue to occur.³¹ As mentioned above, there are a small number of reports of a motor neurone syndrome in HIV positive patients. It is unclear

Box 4: Inherited forms of MND in which a gene has been identified

ALS1

Gain of function mutations in the gene for SOD-1 leading to dominantly inherited ALS which is clinically indistinguishable from the sporadic form.³²

ALS2

Inactivating mutations in a gene called "alsin", a protein with rho-GEF homology and a putative role in cytoskeletal integrity. Leads to recessive primary lateral sclerosis-like picture in three families of Middle Eastern and North African origin.^{34 35}

Proximal spinal muscular atrophy

Inactivating mutations in the survival motor neurone gene leading to recessive spinal muscular atrophy with onset in infancy (Werdnig-Hoffman disease) or childhood to adult life (Kugelberg-Welander syndrome).¹⁵ Survival motor neurone has a role in ribonucleoprotein metabolism.³⁶

Spinal muscular atrophy with respiratory distress

Neonatal spinal muscular atrophy with diaphragm involvement. Recessive mutations in a gene with RNA binding and helicase activity.³⁷

X-linked bulbospinal neuronopathy

Kennedy's disease: bulbar spinal muscular atrophy with sensory neuropathy and androgen insensitivity. Due to gain of function mutations in the androgen receptor gene.¹⁴

whether this is due to direct viral tropism for motor neurones or an opportunistic infection.

The only forms of MND in which a clear cause has been established are the genetic variants listed in box 4. In addition to these diseases there are numerous other inherited forms in which linkage has been established but no gene has yet been identified. Approximately 10% of cases are familial, usually with dominant inheritance. Of these cases, approximately 20% are due to mutations in the gene for superoxide dismutase type 1 (SOD-1).³² Over 100 different mutations in the SOD-1 have been found and these can lead to changes throughout the protein. Despite the obvious assumption that disruption of SOD-1 would lead to motor neurone degeneration through a reduction in free radical scavenging, all the evidence points instead to a toxic gain of function mechanism.³³ It would appear that mutant SOD-1 protein leads to a failure in the normal protein chaperoning mechanism and subsequent degeneration of the motor neurone. Phenotypically there is no recognisable difference between SOD-1 related and sporadic ALS, raising the possibility that a greater understanding of the mechanism of cell death may shed light on the pathogenesis of sporadic disease. Other forms of genetically determined motor neurone degeneration are listed in box 4.

It will be evident from this list that motor neurones are vulnerable to interference with a number of disparate metabolic pathways that do not appear to cause disease in other systems. The exact reasons for this selective vulnerability are not clear but it seems likely that the following factors contribute:

- (1) The extreme length of these cells imposes a high metabolic demand and necessitates specific adaptations to facilitate protein transport.
- (2) Pathological evidence would suggest that degenerating motor neurones in ALS show defects in protein handling. Whether this is a primary element in the pathogenesis or an epiphenomenon is unclear
- (3) Motor neurones may be specifically vulnerable to defects in glutamate metabolism and to oxidative stress.³⁸

Figure 1 is a schematic representation of potential factors in the pathology of MND/ALS. In this model it is presumed that

some as yet undefined triggering event acts on a background of susceptibility factors. Most of the molecular and cellular features of the disease for which there is good evidence belong to the series of events which occur downstream of the initiation of motor neurone death.

MANAGEMENT

People with MND and their carers have complex needs which can only adequately be delivered by a multidisciplinary team experienced in the management of progressive neurological disability. This should normally include a physiotherapist to advise on mobility, postural support, and prevention of contractures; a speech and language therapist to assess swallowing and provide communication aids; an occupational therapist to provide aids to maintain function (wheelchair, mobile arm supports, etc); a dietitian to advise on maintaining weight and percutaneous endoscopic gastrostomy feeding. Liaison with patient support groups such as the Motor Neurone Disease Association (www.mnda.org) in the UK is valued by most patients and their families. For a full list of national organisations see www.alsmndalliance.org. Early contact with palliative care services and discussion of end of life decisions is an important element of care. In some areas palliative care physicians provide most of the care for MND patients once the initial diagnosis is confirmed.

Disease modifying drug treatments

The only drug licensed for the treatment of MND is riluzole, which was designed as a specific glutamate antagonist. In two large randomised trials of patients with the ALS form of MND, the drug was shown to prolong tracheostomy free survival by 3–6 months.^{39–41} It is not known whether this effect extends to non-ALS forms of MND or if specific subgroups of patients get more prolonged survival as the follow up period for these trials was only 18 months. As yet unpublished retrospective analyses of data from large numbers of patients taking the drug have suggested that the effect in prolonging survival may be more than the initial trials suggested but these data are confounded by the general improvements in the care of patients with ALS that has occurred over the last decade, notably greater access to specialist clinics and increased use of percutaneous endoscopic gastrostomy feeding and non-invasive ventilation. Approximately 10% of patients stop the drug because of side effects, principally gastrointestinal intolerance and asthenia. Overall, approximately 50% of patients are reported to be taking the drug, which probably reflects both patients' and physicians' perceptions of the modest effect on survival. Riluzole does not produce an improvement in symptoms. Other drugs which have been the subject of clinical trials in recent years in ALS but for which there is no evidence of benefit include high dose vitamin E, gabapentin, nerve growth factors such as brain derived neurotrophic factor and insulin-like growth factor-1, and immunomodulatory treatments.⁴² Perhaps of concern for the identification of new drugs for clinical trials is the observation that all of these agents showed benefits in animal models or cell culture systems. Despite lack of evidence many patients are taking vitamin E and creatinine. Future therapies will depend on a greater understanding of the pathogenesis but trials of stem cell therapy in animal models of MND are currently exciting much interest.

Treatment of specific symptoms

It is not widely appreciated, outside of specialist clinics, that there are a number of symptoms associated with MND which are highly amenable to treatment. The aim of these interventions is primarily palliative and aimed at maintaining quality of life rather than to prolong the duration of the illness.

Weight loss is universal in MND patients. It occurs even before calorific intake becomes limited by dysphagia and is

Figure 1 Pathogenesis of MND. Most of what we know about the biological events in the pathogenesis of ALS occur downstream of the initial motor neurone injury. The predisposing factors and the initial trigger to injury are poorly understood.

Box 5: Principles of management of ALS/MND

- Multidisciplinary approach.
- Patient and carer support groups.
- Nutrition.
- Respiratory care.
- Palliative care.
- Drug therapy.

due in part to loss of muscle mass. Careful monitoring by a dietitian and early institution of percutaneous endoscopic gastrostomy feeding is widely believed to improve quality of life and alleviate distress, though there are no randomised trials of this intervention. It is important to appreciate that it does not reduce the risk of aspiration

A number of *respiratory symptoms* occur in ALS patients including dyspnoea, orthopnoea, as well as symptoms due to carbon dioxide retention (daytime somnolence, morning headache, lack of restorative sleep, frequent nocturnal waking). Panic attacks are also very common and have a mixed aetiology but usually include some element of laryngospasm and a feeling of not being able to take a good breath. Patients often fear that they will choke to death but this is extremely rare. Panic attacks can be treated with benzodiazepines but these drugs can be hazardous in patients with incipient type II respiratory failure. The most appropriate methods for monitoring patients with ALS are still being established.⁴³ Vital capacity, lying and sitting, is the most practical and frequently used test in the outpatient clinic setting but is unreliable in patients with significant bulbar weakness. Many patients with ventilatory failure from ALS benefit symptomatically from non-invasive ventilation.⁴⁴ Close cooperation with colleagues in respiratory medicine is essential and appropriate patient selection is vital. Fears that this inevitably leads to pressure to proceed to tracheostomy and invasive mechanical ventilation have not proved to be justified in the UK but there is considerable international variation in the practice of long term ventilation. The effect on carers of people with MND should be considered carefully. Inadvertent emergency ventilation by medical teams unfamiliar with the patient's diagnosis and wishes is a disaster for all concerned.

Cramps occur in most patients at some point in the disease but often wane with time and rarely need treatment. *Spasticity* can be a considerable problem leading to pain and reduction in mobility. Physiotherapy has a role, but some patients need antispasticity agents such as baclofen or tizanidine. Botulinum toxin may have an occasional role in specific situations such as jaw spasm which can lead to problems in feeding, articulation, and contribute to panic attacks.

Drooling (sialorrhoea) causes dehydration, social embarrassment, and sore lips. Transdermal hyoscine patches can be very effective without resulting in drowsiness. Botulinum toxin injections into the salivary ducts or irradiation of the salivary glands are also occasionally used successfully,⁴⁵ but the former may be hazardous and requires expertise.

Emotional lability or "pseudobulbar affect" are slightly inaccurate terms for the commonly observed tendency of patients with corticobulbar involvement to laugh or cry inappropriately. The origin of this symptom is not precisely understood but it is not necessarily associated with an emotional experience and should not be interpreted as a sign of depression (see below). While it is slightly commoner in patients with cognitive involvement, it is important to appreciate that most patients with this symptom are cognitively normal. It is often a transient phenomenon that resolves over several months, but if socially embarrassing often responds well to tricyclic antidepressants.

Depression is, not unnaturally, commoner in patients with a progressive, disabling, and terminal illness. The decision to treat must be balanced by the acknowledgement that patients with a grief reaction to their illness are going through a normal psychological process with many of the features of a classical bereavement reaction. Therefore supportive counselling is as important as drug therapy.

THE FUTURE

Although described in the mid-19th century, ALS-MND has proved to be one of the most puzzling neurodegenerative diseases and remains largely untreatable. Much of our knowledge of the pathogenesis of MND comes initially from analysis of postmortem material in which the disease process is advanced and many of the changes reflect the end stage of a cascade of metabolic derangements resulting in motor neurone degeneration. More recently the identification of specific genes causing MND and the creation of animal models with which to study the early events in motor neurone degeneration offers a more realistic hope of identifying the set of factors which make motor neurones peculiarly vulnerable. The underlying assumption with this approach is that the genetic forms of MND are sufficiently like sporadic ALS which is a much commoner problem. Most patients with MND have probably lost a very significant proportion of motor units by the time they are seen by a neurologist and effective treatment and arrest of the process of degeneration will require a precise profile of the molecular events that occur early in the disease process. Ultimately we need to be able to identify those individuals at risk of developing the disease in the first place. Once the disease has advanced to the point of significant functional impairment restorative treatments will have to be

developed. The current hope is that stem cells of neural or extraneural origin might be modified in vitro to differentiate into neurones that would migrate to sites of motor neurone loss and form functional connections to restore the motor pathways lost in MND. In the shorter term there is an urgent need for new therapeutic agents to emerge. Current knowledge would suggest that, whatever the initial insult triggering the disease, a number of biochemical pathways are activated downstream leading to motor neurone death, perhaps through apoptosis. By analogy with previously medically intractable disease such as haematological malignancy, it may be that combination chemotherapy with riluzole and other drugs will lead to progressive improvements in survival. It is important that quality of life, not just duration of survival, is part of the measure of effectiveness of drug regimens.

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SELF ASSESSMENT QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

Q1. The following are motor neurone disorders:

- (A) Primary lateral sclerosis
- (B) Huntington's disease
- (C) Amyotrophic lateral sclerosis
- (D) Spinal muscular atrophy
- (E) Lathyrism

Q2. Motor neurone disease:

- (A) Shows marked variations in incidence between different regions of the world
- (B) Is commoner in men
- (C) Carries a worse prognosis in women
- (D) Carries a worse prognosis if onset is in the lower limbs
- (E) Is associated with a family history in 10% of cases

Q3. Mutations in the gene for superoxide dismutase (SOD) type 1:

- (A) Cause a form of MND/ALS which is readily distinguishable clinically from sporadic disease
- (B) Lead to motor neurone death through loss of free radical scavenging activity
- (C) Only account for a minority of cases of dominantly inherited ALS
- (D) Occur in a specific region of the SOD gene which is critical for its function in oxidative metabolism
- (E) Are also associated with some forms of Parkinson's disease

Q4. The following treatments prolong life:

- (A) Glial derived neurotrophic factor
- (B) Riluzole
- (C) Graded physiotherapy
- (D) Invasive mechanical ventilation
- (E) High dose vitamin E

Q5. The following are inconsistent with a diagnosis of MND:

- (A) The presence of any abnormality on the MRI scan
- (B) A creatine kinase level of 1500 IU
- (C) Dementia
- (D) Sensory changes on nerve conduction studies
- (E) Involvement of eye movements

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ANSWERS

Q1: (A) T, (B) F, (C) T, (D) T, (E) T.

Primary lateral sclerosis and amyotrophic lateral sclerosis are forms of typical MND. The spinal muscular atrophies are a group of inherited disorders of the lower motor neurone which are usually slowly progressive. Huntington's disease (chorea, personality change) does not involve motor neurones. Lathyrism is an epidemic form of upper motor neurone syndrome seen in India and due to ingestion of a toxic chickling pea.

Q2: (A) F, (B) T, (C) T, (D) F, (E) T.

MND seems to have a uniform incidence in developed countries and there is an unexplained 1.6:1 male to female ratio. Females have a slightly worse prognosis, probably because a bulbar disease onset occurs in 50% of females compared with 25%–30% of males. The longer the disease remains confined to a specific region such as the legs, the better the overall prognosis.

Q3: (A) F, (B) F, (C) T, (D) F, (E) F.

Mutations in SOD-1 only cause ALS (20% of familial cases) and have not been associated with any other neurodegenerative disease. The SOD-1 form of ALS is clinically indistinguishable from sporadic ALS. The disease appears to result from a disorder of protein handling and SOD-1 free radical scavenging appears to be normal in most cases. The mutations are scattered throughout the gene and not confined to any functional motif of the protein.

Q4: (A) F, (B) T, (C) F, (D) T, (E) F.

Riluzole is the only drug which has been shown in clinical trials to have any effect on disease duration. Invasive mechanical ventilation will prolong life by several years but the progression of paralysis (and possibly dementia) continues. For this reason few patients wish to pursue this as an option.

Q5: (A) F, (B) F, (C) F, (D) T, (E) T.

MRI abnormalities (especially MRI spectroscopy) due to corticospinal tract degeneration do occur in MND. Clearly the presence of a structural lesion in the appropriate place raises an alternative explanation for the clinical presentation of MND. A creatine kinase of >1000 IU is unusual but can sometimes be seen with a lot of active denervation. Frank dementia occurs in 3% of patients. Marked sensory abnormalities on nerve conduction studies should lead to the diagnosis being questioned, as should extraocular muscle weakness which is very rare in MND.