

Motor Neuron Disease

- Motor neuron disease (MND) is a greatly feared diagnosis leading some to seek euthanasia.
- It is the most common progressive condition to cause a combination of upper and lower motor neuron signs.
- MND is a disease of increasing age and is likely to become commoner as the population ages.
- The lifetime risk of MND is about 1 in 400, even though the prevalence is only about 5 per 100,000.
- The average GP sees one case per lifetime; the average neurologist sees one case per month.
- About 1 in 5 survives five years, and 1 in 10 survives more than ten years.
- Although the prognosis is generally poor, there are patterns of MND that generally predict a slower course and longer survival.
- About 1 in 10 people has a family history of MND and a fifth of these carry mutations in the SOD1 gene.
- Other genes for typical MND remain elusive, although some progress has been made.
- Causes for those with sporadic MND remain unknown, although there are many theories.
- Sub-clinical cognitive impairment is common; overt fronto-temporal dementia affects about 5%.
- Multidisciplinary clinics improve quality of life and lead to advances in treatment.
- Riluzole is a drug that has been shown to improve survival consistently in many different study designs.
- Advances in care such as non-invasive ventilation and gastrostomy lead to improved quality of life and extended survival, but may reduce quality of life for carers.

An introduction to MND

Motor neuron disease (MND), also known as amyotrophic lateral sclerosis (ALS), was first described by Charcot in 1869.¹ The classical picture is of progressive

wasting and weakness with brisk reflexes, in the absence of sensory signs and incoordination (Figure 1). The weakness starts in a limb or the bulbar region, and spreads, usually contiguously, over a period of months. Death occurs as a result of respiratory failure, typically within a few years of symptom onset. The dismal outlook of an inevitable progression to complete paralysis leads some to seek euthanasia.

The different types of MND

MND is a result of the degeneration of lower motor neurons in the anterior horn of the spinal cord and brainstem (amyotrophy), and degeneration of the corticospinal motor neurons (described as lateral sclerosis of the spinal cord by Charcot). The nuclei controlling eye movements, and Onuf's nucleus controlling bladder and anal sphincters, are spared.

The amyotrophy and lateral sclerosis components of MND do not always occur simultaneously, and as a result, other diagnostic categories exist. Progressive muscular atrophy describes the condition of pure lower motor neuron loss, and primary lateral sclerosis the condition of pure upper motor neuron loss. People with these patterns of MND do not always progress to classical amyotrophic lateral sclerosis, and it is more difficult to be certain that diagnostic mimics have been excluded. In some cases, the disease remains predominantly bulbar, in which case the label used is bulbar palsy (or pseudobulbar palsy if there are only upper motor neuron findings) (Table 1).

Clinical features outside the motor system

Emotional lability, often associated with pseudobulbar palsy, can be difficult for family members to deal with, and is also embarrassing and therefore socially isolating. Frontal lobe impairment is not uncommon. At its mildest this is detectable as word-finding difficulty,² but in about 5% of cases is severe enough to be a fron-



Ammar Al-Chalabi is a Senior Lecturer in Neurology and Complex Disease Genetics at King's College Hospital. He is also a Visiting Scientist in Neurology at Massachusetts General Hospital, and an Instructor in Genetics of Complex Human Diseases at Cold Spring Harbor Laboratory. He has been researching motor neuron disease since 1994, first as an MRC Clinical Training Fellow, and more recently as an MRC Clinician Scientist. He has a special interest in finding motor neuron disease genes using whole genome association.

Correspondence to:

Ammar Al-Chalabi, PhD, FRCP, Senior Lecturer in Neurology and Complex Disease Genetics, MRC Centre for Neurodegeneration Research, King's College London, SE5 8AF.

Email: ammar@iop.kcl.ac.uk

Tel: 020 7848 5172,

Fax: 020 7848 5190.

Table 1. The names given to different patterns of ALS

	Bulbar signs	Limb signs
<i>UMN</i>	<i>Pseudobulbar palsy</i>	<i>Primary lateral sclerosis (PLS)</i>
<i>LMN</i>	<i>Bulbar palsy</i>	<i>Progressive muscular atrophy (PMA)</i>
<i>Both</i>	<i>Amyotrophic lateral sclerosis (ALS)</i>	<i>Amyotrophic lateral sclerosis (ALS)</i>



Figure 1. Wasted hands with a typical clawed posture

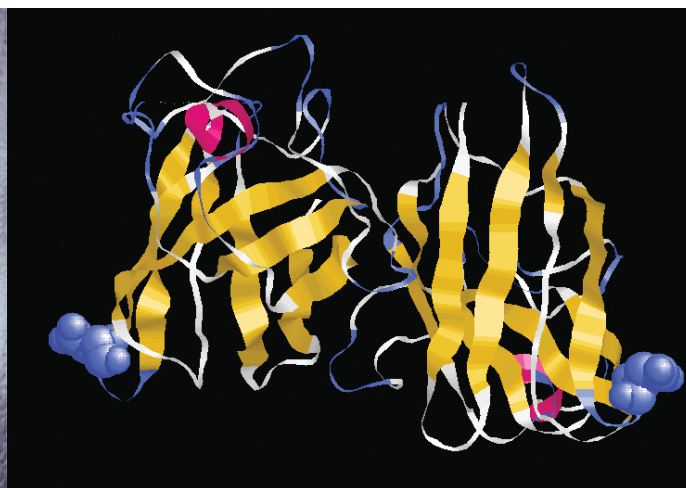


Figure 2. Mutation in the SOD1 molecule, the only known cause of ALS, showing the D90A mutation.

totemporal dementia. The overlap between MND and frontotemporal dementia is becoming increasingly recognised; for example, the two conditions may co-exist within families as a result of the same genetic defect.^{3,4}

Epidemiology, pathology and ideas about causation

MND has an incidence of about 1-2 per 100,000 person years and a prevalence of about 5 per 100,000. The lifetime risk is about 1 in 400, estimated either from death certificates Office of National Statistics⁵ or using population registers.⁶ Men are more at risk than women with a ratio of about 3:2. The peak age of onset is between 56 and 70, depending on the mode of ascertainment. There are no consistently shown environmental risk factors, although taking part in high level sports is probably the most widely accepted, and professional football is the most recent target of blame.⁷

It remains a mystery why motor neurons should bear the brunt of the disease process in MND. One possibility is their highly unusual shape. If the cell body were about 30 yards across, the axon of a typical motor neuron would be about the size of a tube train tunnel connecting London and New York. Pathologically, degenerating motor neurons contain inclusions that stain for ubiquitin, and also accumulations of neurofilaments. It is not clear whether the inclusions and accumulations protect the neuron, poison the neuron, or are simply markers like a gravestone. Neurofilament mutations have been found in MND, and other cytoskeletal defects are known to lead to motor neuron degeneration in both humans and animals. This may be because the cytoskeleton is essential for axonal transport, and the highly unusual shape of a motor neuron makes it vulnerable. Motor neurons also use excitatory pathways rather than the more widespread inhibitory pathways favoured by the rest of the nervous system. Excitotoxicity has therefore been proposed as a mechanism, and there is some evidence to support this idea. A closely related mechanism involving free radicals has also been suggested, and the finding of mutations in a free radical scavenging enzyme, SOD1, has lent support to this idea.⁸ Viruses too

have been implicated,⁹ particularly because another motor neuron disease, polio, is known to be virally mediated.

Genetics

Familial MND (10% of all cases) is usually autosomal dominant. Because it is indistinguishable from sporadic MND, it too shows an increasing risk with age, so some members of an affected family may be below the age of risk and unaffected despite carrying the risk gene. There are at least 12 loci for familial MND with four genes now identified, only one of which is for typical MND: SOD1. Mutations in SOD1 are responsible for about 20% of all familial cases as well as between 1 and 7% of sporadic cases^{8,10} (Figure 2). Genetics is recognised as playing an important part in susceptibility to sporadic disease too with a twin study reporting the genetic contribution to MND as being between 38 and 85%.¹¹ More than 40 candidate genes have been tested for association with sporadic MND, only a few of which have shown replicated association in more than one population: SOD1, NEFH, VEGF and ANG.^{12,13} With advances in genetic techniques, whole genome association studies are now underway and the next few years is likely to see the underlying genetic causes of MND revealed.

Making the diagnosis

There is no diagnostic test for MND, which remains a diagnosis of exclusion. In someone with classical features, progressive disease and EMG findings showing chronic partial denervation, there can be little doubt about the diagnosis once other possibilities have been excluded. In those with less typical features, or disease confined to one or two limbs, it can be more difficult, and it may be necessary to repeat tests a few months later.

Prognosis

The prognosis is generally very poor with survival measured in months to years. Death is from respiratory failure. Those with progressive muscular atrophy or primary lateral sclerosis in general have a slower disease progression. Other clinical features associated with a better than average survival include a younger age at onset of symptoms, disease confined to one or two limbs, and having the so-called

flail arm phenotype in which there is profound symmetrical weakness of the proximal upper limbs with relatively preserved strength elsewhere.¹⁴ The best predictor of a good outcome is however a long delay between symptom onset and review by a neurologist.¹⁵ This is probably because it reflects slowly progressive, milder disease that is as a result more difficult to diagnose. In general, MND continues at the same rate of progression or occasionally plateaus, and so a long referral delay implies a long duration to come. Despite this, even those with poor prognostic factors may still survive more than ten years, so there is hope for everyone.¹⁶

Treatment

Riluzole has been shown in several studies of prospective and retrospective design to be effective in prolonging survival, although the effect is modest and similar to some cancer therapies. Side effects include liver and bone marrow toxicity, dizziness and vertigo, which may interfere with skilled tasks such as driving. Nausea, lethargy and rash may also occur.

Other treatment involves active and aggressive symptom control using medication, for example quinine for cramps, anticholinergics for sialorrhoea, antidepressants for emotional lability, baclofen or tizanidine for spasticity and benzodiazepines and opiates for respiratory failure. These are combined with intervention from the multidisciplinary team with physiotherapy, occupational therapy, speech therapy, dietetic advice, counselling and palliative care. Respiratory failure can also be managed with non-invasive ventilation, which is not suitable for everyone but is effective at prolonging duration and improving quality of life. Similarly, for those with dysphagia, gastrostomy needs to be provided earlier rather than later, and may also improve survival.

Conclusion

The great advances in care and research, particularly over the last ten years, mean that we are chipping away at MND from the top with clinical trials, and from underneath with basic science. Soon a breakthrough in our understanding may lead to a highly effective treatment for this dreaded condition.

References

- Charcot JM & Joffroy A. *Deux cas d'atrophie musculaire progressive avec lésions de la substance grise et des faisceaux antero-latéraux de la moelle épinière*. Archives of Physiology, Neurology and Pathology 1869;2:744.
- Abrahams S. et al. *Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS)*. Neuropsychologia 2000;38:734-47.
- Vance C et al. *Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2-21.3*. Brain 2006;129:868-76.
- Morita M et al. *A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia*. Neurology 2006;66:839-44.
- Table 2 Deaths by age, sex and underlying cause, 2003 registrations. (Office of National Statistics, 2003).
- Johnston CA et al. *Amyotrophic Lateral Sclerosis in an Urban Setting: A Population Based Study of Inner City London*. Journal of Neurology In press (2006).
- Chio A, Benzi G, Dossena M, Mutani R & Mora G. *Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players*. Brain 2005;128:472-6.
- Rosen DR et al. *Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis* [published erratum appears in Nature 1993 Jul 22;364(6435):362] [see comments]. Nature 1993;362:59-62.
- Steele AJ et al. *Detection of serum reverse transcriptase activity in patients with ALS and unaffected blood relatives*. Neurology 2005;64:454-8.
- Jackson M et al. *SOD-1 and sporadic ALS: analysis of 155 cases and identification of a novel insertion mutation*. Annals of Neurology 1997;42:803-6.
- Graham AJ, Macdonald AM & Hawkes CH. *British motor neuron disease twin study*. [Review] [60 refs]. Journal of Neurology, Neurosurgery and Psychiatry 1997;62:562-9.
- Greenway MJ et al. *ANG mutations segregate with familial and 'sporadic' amyotrophic lateral sclerosis*. Nat Genet 2006;38:411-3.
- Lambrechts D et al. *VEGF is a modifier of amyotrophic lateral sclerosis in mice and humans and protects motoneurons against ischemic death*. Nat Genet 2003;34:383-94.
- Hu MT, Ellis CM, Al-Chalabi A, Leigh PN & Shaw CE. *Flail arm syndrome: a distinctive variant of amyotrophic lateral sclerosis* [letter]. Journal of Neurology, Neurosurgery and Psychiatry 1998;65:950-1.
- Turner MR et al. *Prognostic modelling of therapeutic interventions in amyotrophic lateral sclerosis*. Amyotrophic Lateral Scler Other Motor Neuron Disord 2002;3:15-21.
- Turner MR, Parton MJ, Shaw CE, Leigh PN & Al-Chalabi A. *Prolonged survival in motor neuron disease: a descriptive study of the King's database 1990-2002*. J Neurol Neurosurg Psychiatry 2003;74:995-7.