

Ministry of Defence

Synopsis of Causation

Motor Neurone Disease

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September 2008

Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1 **Motor neurone disease** (MND) is a term applied to a group of neurological disorders of unknown aetiology in which there is selective loss of function of the [upper](#) and/or [lower motor neurones](#) controlling the voluntary muscles of the limbs or the [bulbar](#) region. In the USA, the equivalent term is [amyotrophic lateral sclerosis](#) (ALS), but in the UK this name is reserved for the commonest variant which involves both upper motor neurone and lower motor neurone lesions and represents about 85% of all cases.
- 1.2 Motor neurone disease (UK definition) can arise from a mixture of upper and lower motor neurone lesions or from either type alone. There is no sensory involvement.
- 1.3 Purely upper motor neurone lesion disease is called **primary lateral sclerosis** and purely lower motor neurone degeneration is known as **progressive muscular atrophy**. The disease can also present as a **progressive bulbar palsy**.
- 1.4 Occasionally motor neurone disease occurs in combination with other conditions, usually dementia or Parkinson's disease, in which case it is called "**ALS plus**".
- 1.5 The incidence of MND is between 1.8 and 2.2 cases per 100,000, leading to a prevalence of 4.0 to 4.7 per 100,000 population. This represents about 2,000 cases in the UK. It can occur at any age from teens to late 80s, but onset is most frequent between 55 and 75 years. It makes up 4% of all non-traumatic causes of [tetra-](#) and [paraparesis](#). There is a slight male preponderance of between 1.5 and 2.0:1. The reported frequency of MND has risen in recent years,¹ but this may be attributable to more accurate diagnosis.
- 1.6 About 5% of cases seem to be inherited as an [autosomal dominant](#) disorder. These tend to have a slightly lower age of onset at about 45 years and an equal sex incidence.
- 1.7 **Criteria for diagnosis.** The El Escorial criteria were established by the World Federation of Neurology (WFN) in 1994 and revised by the WFN Research Committee on Motor Neurone Diseases in 1998 in an effort to increase sensitivity.² However, the validity and reproducibility of the diagnosis based on those criteria has been questioned.^{3,4} It seems likely that training in their use will improve the validity. The WFN Research Group on Motor Neurone Diseases revised its criteria again in 2000.⁵

2. Clinical Features

2.1 Presentation is variable. There are variations of the disease, and presentation depends on which neurones are involved:

- **Progressive bulbar palsy** gives pure [bulbar](#) involvement. It can be lower motor neurone leading to a true bulbar palsy or [upper motor neurone](#) producing what is known as a pseudobulbar palsy
- **Primary lateral sclerosis** produces upper motor neurone disease affecting the limbs
- **Progressive muscular atrophy** results from pure lower motor neurone disease
- Adult onset **spinal muscular atrophy** includes a wide range of primary motor neurone diseases classified by age of onset, pattern of inheritance and distribution of weakness

About 75 to 80% of patients present with limb involvement, the first part to be affected usually being the hands. The remaining 20-25% have bulbar lesions.

2.2 **Presenting complaints.** The onset is slow and insidious. The patient will usually be seen first in primary care with one or more of the following:

- Muscular weakness of the hands, arms, legs or face
- Difficulty with fine movements such as doing up buttons
- Foot drop, with the toe scuffing the ground on walking, which causes tripping and stumbling
- Muscle wasting
- Muscle cramps
- [Fasciculation](#) of muscles
- [Spasticity](#) (presents as stiffness and the limbs feel “heavy”)
- Difficulty chewing and swallowing, or drooling
- Difficulty with speech and slurring or alteration in the quality of the voice
- Cranial nerve lesions of bulbar or pseudobulbar palsy, which usually produce progressive [dysarthria](#), often followed by [dysphagia](#)
- Weakness of the respiratory muscles, which can cause [dyspnoea](#) or [orthopnoea](#)
- Certain pathways are usually spared. These include all sensory pathways and the oculomotor, trochlear, and abducens nerves in the brainstem. These are the nerves that control movements of the eyes. In the spinal cord, this applies to the [posterior columns](#) and spinocerebellar tracts as well as to the nuclei that control the sphincters of the bowel and bladder, and sexual function

2.3 **Examination** will reveal abnormalities in the nervous system only, unless immobility has caused additional problems like stiffness of joints. Inspection may reveal muscular wasting, often of an asymmetrical distribution. [Fasciculation](#) may be present. If it affects the tongue, the smaller muscle units produce a finer pattern called fibrillation.

2.3.1. **Weakness** may be diffuse, variable in severity and asymmetrical. Coordination is normal within the limitations of muscular power. Fine movements may be difficult.

- 2.3.2. Since the condition can consist of a mixture of upper and lower motor neurone lesions, **the pattern of tendon reflexes may be mixed**. Reflexes are usually brisk in the early stages but become suppressed as the disease advances. This is one of the few diseases in which a suppressed ankle reflex and an extensor plantar response may coexist. Other reflexes such as finger jerks and the jaw jerk may be enhanced.
- 2.3.3. The presence of bulbar weakness manifesting in the voice or tongue is a risk factor for developing aspiration. Detailed speech therapy review and videofluoroscopy is necessary to quantify this risk.
- 2.3.4. **The sensory system** should show no abnormality. Patients sometimes complain of numbness but sensory loss is not substantiated on objective testing.
- 2.4 **Progression is inevitable**. Locomotion becomes more difficult. Wasting, fasciculation and muscle cramps become more pronounced and speech more disjointed and laboured. Palatal weakness produces a nasal quality of speech which sounds strained and has a strangled quality. Sphincter control is usually maintained, although weakness of associated muscles may produce urgency of micturition and constipation. Chewing and swallowing may be difficult. Drooling is common. Food tends to become lodged in the cheeks and may need to be removed manually. Liquids are more troublesome than solids. Death results from weakness of respiratory muscles and lack of the swallowing reflex leading to aspiration and lower respiratory tract infection.
- 2.5 **Higher functions** are usually well preserved, although there is a subgroup of patients who develop fronto-temporal impairment leading to progressive decline in cognitive function. Also, some people with pseudobulbar symptoms have an exaggerated emotional response of separate aetiology, resulting in frequent and rapid alterations in emotions. Episodes of intense laughter may be followed immediately by tears, and the response does not correspond to any apparent social or psychosocial situation. Specific testing may reveal rather more impairment of higher function than is obvious.⁶
- 2.6 Some of the features of the disease are not directly caused by the primary pathology but are the result of the disease process.
- Loss of weight is very common and results from dysphagia. As it is associated with a poor prognosis, a nasogastric tube may be inserted short-term, but for long-term management enteral feeding via a percutaneous [endoscopic gastrostomy](#) (PEG) or other such devices gives better results
 - Failure to clear the airways due to muscular weakness can result in chest infections
 - This may be an indication for mechanical ventilation. Simply giving oxygen may reduce the respiratory drive and aggravate [hypercapnia](#)
 - [Tracheostomy](#) may be required to aid ventilation and to protect the upper airways
 - Pain can be caused by a number of mechanisms including muscle spasms or altered joint biomechanics, as well as immobility and pressure
 - This chronic progressive and devastating disease does not normally impair cognitive function and so psychological problems, particularly of a depressive nature are likely
- 2.7 **Diagnosis** is essentially clinical, but the EMG characteristically shows evidence of denervation and reinnervation. This is helpful in confirming clinical impressions,

especially in view of the prognostic implications of the diagnosis. There is no specific blood or imaging modality to confirm the diagnosis, although various tests including magnetic resonance imaging (MRI) of the brain and spinal cord may be employed to exclude other diseases such as multiple sclerosis. Neuroimaging and electromyography can reduce the time from presentation of the patient to reaching a firm diagnosis.⁷ Genetic testing may be useful in the uncommon familial types.

2.8 **Biopsy of muscle** may provide supporting evidence.

2.9 **Differential diagnosis.** The diagnosis is based on the El Escorial Criteria, but may still be made if these are not entirely fulfilled. On the other hand, because of the prognostic implications, the diagnosis should not be made without good evidence.⁸

Other diseases to consider are:

- Multiple sclerosis
- Diabetic amyotrophy
- Cervical myelopathy
- Poliomyelitis
- Inflammatory muscle conditions such as polymyositis
- Thyrotoxicosis or Cushing's disease
- Syringomyelia
- Mercury or lead poisoning
- Spinal cord compression
- Vitamin B12 deficiency
- HIV infection

3. Aetiology

- 3.1. Despite increasing knowledge, the cause of MND is unknown, with the exception of the occasional inherited form. Approximately 5 to 10% may be **familial** and appear to be inherited as an [autosomal dominant](#) condition. Some of these have a mutation in the gene Cu/Zn superoxide dismutase on chromosome 21.⁹ This accounts for approximately 20% of familial cases and 2% of all cases. The familial and sporadic cases have a similar clinical picture. A much rarer mutation leads to an [autosomal recessive](#) primary lateral sclerosis-like picture that has been described in three families of Middle Eastern and North African origin. Proximal spinal muscular atrophy can be due to a recessive disorder with onset in infancy (Werdnig-Hoffman disease) or childhood to adult life (Kugelberg-Welander syndrome). Neonatal spinal muscular atrophy with diaphragm involvement is another rare recessive disorder. Kennedy's syndrome is bulbar spinal muscular atrophy with sensory neuropathy and androgen insensitivity due to mutations in the androgen receptor gene. It is linked to the X chromosome.¹⁰
- 3.2. Various forms of **autoimmune** phenomena have been considered as aetiological factors, but the evidence is not compelling, and therapies designed to treat autoimmune disease have not been shown to have any beneficial effect.¹¹
- 3.3. **Occupational and environmental factors**
 - 3.3.1. An American study found results consistent with previous reports suggesting a potential role for **lead exposure** in the causation of ALS.¹² Chemicals used by **leather workers** have also been implicated. Another study suggested an association between MND and **agricultural chemicals** but not metals and solvents in men.^{13,14} Many environmental influences, including multiple immunisations have been considered, but there is little supporting evidence.^{15,16}
 - 3.3.2. In an epidemiological study, **commercial pilots and navigators** were found to have a relative risk of 2.2 of developing MND.¹⁷ There is a significant degree of uncertainty in the accuracy of this figure, however, and this observation has not been confirmed.
 - 3.3.3. One study has proposed that patients with MND are more likely to have a history of being athletic and slim,¹⁸ and attention has been drawn to the development of the disease in **athletes**. In the USA, boxer Ezzard Charles, and baseball players Catfish Hunter and Lou Gehrig all died of MND. In American football, three players from the San Francisco 49ers were diagnosed with the condition in the 1980s, and Glenn Montgomery of the Seattle Seahawks died of it in 1998. However, the numbers involved are too small to provide meaningful data.
 - 3.3.4. It has been suggested in a study from Italy that **professional footballers** may have an increased risk of MND,¹⁹ following an earlier judicial report for the football association from the same region. The risk appeared to increase with time, and the authors proposed that extensive vigorous exercise could be responsible. No other studies have replicated this finding, although some are still in progress. A recent Industrial Injuries Advisory Council (IIAC) position paper on sporting injuries concluded that the published literature was

conflicting and that there was no consistent evidence to support an occupational basis for the development in MND in sportsmen and sportswomen.²⁰

- 3.3.5. **Gulf War veterans and military service.** A debate has continued over several years about the possibility of a link between MND and Gulf War service. Two epidemiological studies that sought to explore this issue were published in 2003. One report concluded that military personnel who were deployed to the Gulf region during the Gulf War period (1990-91) experienced a greater post-war risk of MND than did servicemen who were not deployed to the region.²¹ The other report concluded that the observed incidence of MND in young Gulf War veterans (i.e. those aged < 45 years) exceeded the expected incidence, as estimated by US national mortality statistics.²² Both studies suggested an approximately twofold increased risk of MND in Gulf War veterans.
- 3.3.6. However, the conclusions drawn in these studies have been challenged and potential methodological flaws have been raised.²³ The research involved relatively few MND diagnoses and doubt has been cast of the validity of findings that are based on small numbers of cases.²⁴
- 3.3.7. A further study published in 2005 broadened the debate. This involved a cohort of over 500,000 men (military and non-military) who were followed as part of the American Cancer Society Cancer Prevention Study between 1989 and 1998. The study concluded that men who served in the US military had an increased death rate from MND (RR 1.53, 95% CI 1.12 – 2.09) compared to those who did not serve. The increase appeared to be largely independent of the branch of service and the time period served, and it is noteworthy that the military service involved had been completed before the first Gulf War. No satisfactory explanation has yet emerged for the mechanism by which military service might influence the incidence of MND. However, a number of exposures have been put forward for further investigation including toxic agents, various infections, inhalation of aerosolised lead, traumatic injury, and intense physical activity.²⁵ Although this research also has methodological limitations, the data suggest that there is no environmental exposure specific to the Gulf War that is responsible for an increased risk of MND. It also suggests that the increased risk of MND associated with military service is low and is not expected to rise dramatically in the future.²⁶
- 3.4. **Infection.** Hypotheses regarding persistent antecedent poliomyelitis and/or persisting enteroviral infection have been put forward,^{27,28} but there is little direct evidence for a causative effect. There are a small number of reports of a motor neurone syndrome in HIV positive patients. It is unclear whether this is due to a direct effect of the virus on motor neurones. This ALS-like syndrome in HIV may be reversible with treatment.²⁹
- 3.5. **Electrocution** can sometimes lead to isolated cases and whilst this appears to be a genuine biological phenomenon, it is very uncommon.³⁰
- 3.6. Some **specific types** of MND-like syndromes also occur in Africa or India, especially in periods of drought.

- 3.6.1. **Konzo** tends to affect mostly the lower limb, and hip mobility is severely impaired. Muscle power in the upper limb is normal but with impairment of fine movement.³¹
- 3.6.2. **Lathyrism** usually affects males between 10 and 14, especially during severe drought. There appears to be some risk associated with the use of grasspea food with traditional handmade clay pots in Ethiopia.³²
- 3.6.3. There was a particularly high incidence of MND in **Guam**, particularly in the 1950s. The rate has, however, fallen markedly in the last 50 years, which suggests that the cause, though not identified with certainty, was environmental rather than genetic. Neurological illness was manifested as MND, Parkinson's disease, dementia, or a combination of these three conditions, suggesting a variant that it is not typical MND. Patients in Guam with MND but not the parkinsonism-dementia complex were found to have elevated levels of cadmium, but not of 7 other metals that were assayed.³³ This illness may be peculiar to Guam and not relevant to the rest of the world.
- 3.6.4. A similar increase in incidence of parkinsonism and MND was seen in **Guadeloupe** in the late 1990s, which may have been associated with exposure to tropical plants containing mitochondrial complex I inhibitors such as quinolines, acetogenins and rotenoids.

4. Prognosis

- 4.1 Motor neurone disease is a chronic and progressive disease that is ultimately fatal. Although there is no curative treatment, the National Institute for Clinical Excellence (NICE) has allowed the prescription of the antiglutamate, riluzole under the supervision of a neurologist.³⁴ This does have a disease-modifying effect. The cause of death is usually respiratory infection or failure.
- 4.2 Symptomatic support is very important, with input from physiotherapy, occupational therapy and speech therapy, and later from palliative care services.
- 4.3 The overall 5-year survival rate from time of diagnosis is 25%.³⁵ The expected survival after diagnosis is 2 to 3 years for progressive bulbar palsy, 3 to 5 years for amyotrophic lateral sclerosis and 3 to 10 years for progressive muscular atrophy.³⁶ Average survival is about 3 years from diagnosis.³⁷
- 4.4 Some patients have a more chronic form of the disease. Survival is increased by aggressive management of airways and the respiratory system. Ventilation, whether invasive or non-invasive, prolongs survival if there is a steady decline in respiratory function. However, mechanical ventilation with a cuffed endotracheal tube can lead to a situation in which there is profound weakness without the patient developing the terminal respiratory complications of the condition. Prognosis tends to be worse in older patients and in those with a predominantly bulbar form of the disease.

5. Summary

- 5.1 **Motor neurone disease** is a chronic and progressive neurological disease of unknown aetiology, although 5-10% of cases appear to be inherited as an autosomal dominant variation, with 20% of these cases being linked to a deficiency of superoxide dismutase.
- 5.2 In the USA it is called **amyotrophic lateral sclerosis**, although in the UK this name is reserved for the commonest variant which involves both upper motor neurone and lower motor neurone lesions and represents about 85% of all cases.
- 5.3 The disease can be classified according to the manner of its presentation:
 - Progressive bulbar palsy
 - Primary lateral sclerosis
 - Progressive muscular atrophy
 - Spinal muscular atrophy
- 5.4 Diagnosis is essentially clinical. It is based on motor symptoms only with a mixture of upper and lower motor neurone features (in ALS) and no objective sensory loss. The diagnosis may be confirmed by characteristic electrophysiological studies and the absence of abnormalities on imaging.
- 5.5 Pathways to the external ocular muscles and to the sphincters of bowel and bladder are usually preserved, as are the spinocerebellar tracts and posterior columns.
- 5.6 Management is purely supportive.
- 5.7 The rate of progression of the disease is variable, but the 5-year survival rate is only 25% with about half of all the patients dying within approximately 3 years from presentation.

6. Related synopses

Multiple Sclerosis

Parkinson's Disease

7. Glossary

amyotrophy	The wasting of muscle fibres caused by loss of their nerve supply.
atrophy	A wasting process.
autosomal dominant	Requires that only one parent need have the trait (characteristic) in order to pass it to the offspring.
autosomal recessive	Requires that both parents need have the trait in order to pass the condition to the offspring.
bulbar	Relating to the medulla oblongata which is part of the brain stem.
dysarthria	Difficulty in speaking caused by mechanical dysfunction.
dysphagia	Difficulty or pain with swallowing.
dyspnoea	Difficulty in breathing.
endoscopic	Performed via an endoscope. This is a fiberoptic instrument for inspection of the inside of the bowel.
fasciculation	Spontaneous twitching of small groups of muscle fibres. It is typical of lower motor neurone lesions or intrinsic disease of muscle.
gastrostomy	Creating a connection between the stomach and the surface of the body, usually for the purpose of feeding.
hypercapnia	Raised level of carbon dioxide in arterial blood.
lower motor neurone	A nerve cell with its body in the spinal cord which conducts impulses received from an upper motor neurone to a muscle.
orthopnoea	Breathing difficulty which occurs when lying flat.
paraparesis	Paralysis of the lower limbs.
posterior columns	The back part of the spinal cord which carries the fibres associated mainly with awareness of joint and body position.
rostral	At a higher level.
sclerosis	Pathological hardening or thickening of tissue.
spasticity	Rigidity of muscles associated with upper motor neurone lesions. Lower motor neurone lesions tend to produce flaccidity.
tetraparesis	Paralysis of all four limbs.

tracheostomy	Operation to insert a tube into the trachea. It facilitates mechanical ventilation and protects the airways from inhalation of saliva or food.
upper motor neurone	A nerve cell with its body in the brain which transmits impulses to lower motor neurones in the spinal cord.

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