

Motor neuron disease

Motor neuron disease (MND) is a devastating disease with a significant morbidity and shortened life expectancy. The needs of patients with MND are complex and hence a range of health professionals may be involved in their care, including GPs, geriatricians, chest physicians and palliative care physicians. This article aims to educate the non-neurologist about the clinical features of the disease, current concepts about its pathogenesis, prognosis and treatment strategies.

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Motor neuron disease (MND) is a disabling and inevitably fatal disease which affects adults in later life, who are often fit and active. It is the third commonest neurodegenerative disease after Alzheimer's disease and Parkinson's disease. The annual incidence is two per 100,000; high mortality leaves a prevalence of 5–7 individuals per 100,000 population. In the UK 1200 new cases are diagnosed each year; a GP is likely to see 2–3 patients in his career.¹

Presentations and diagnosis

The primary pathology in MND is progressive degeneration of both upper and lower motor neurons in the nervous system. Degeneration of bulbar motor nuclei and anterior horn cells causes weakness and atrophy of respective muscles. The usual presentation is with speech and swallowing problems; cramps, twitching, clumsiness in the limb muscles; loss of manual dexterity, foot drop or unprovoked falls. Combination of upper and lower

motor neuron signs, in more than one region eg. a weak-fasciculating and spastic tongue combined with foot drop, and absence of sensory signs, are very helpful pointers to the diagnosis. The disease is commonly more focal in onset and hence diagnosis or referral to a specialist is usually delayed for several months.

Motor neuron disease may take the form of Amyotrophic Lateral Sclerosis (ALS—combination of upper and lower motor neuron signs), Primary Lateral Sclerosis (PLS—predominantly upper motor neuron signs), Progressive Bulbar Palsy (PBP—signs limited to bulbar muscles) or Progressive Muscular Atrophy (PMA—predominantly lower motor neuron signs). Bulbar onset is more common in women and in elderly patients, with 43% of those above 70 presenting with bulbar symptoms.² Flail arm syndrome, flail leg syndrome and ALS with multi-system involvement (eg. ALS-dementia-parkinsonism complex) are also considered MND variants as they share the same molecular and cellular pathology but have a slower

course. Traditionally described as a disorder of motor neurons, MND is now being recognised as a multi-system disorder with extrapyramidal, cerebellar and cognitive involvement. About 30% of the patients may have cognitive impairment on neuropsychological testing with overt frontotemporal dementia in up to 5% of the patients. Autonomic dysfunction such as loss of bladder control and erectile dysfunction are highly unusual and hence alternative explanation should be sought.

The diagnosis of MND is largely clinical and by exclusion. There is no diagnostic test or biomarker for MND. Patients with suspected MND generally undergo a range of investigations including serological tests, CSF studies, MRI scan (of the brain and spinal cord) and electromyography (EMG), along with genetic tests. It is important to rule out disorders which may mimic MND and may have more favourable prognosis or are amenable to treatment (eg. pure motor neuropathies, inclusion body myositis). The EMG (motor and sensory nerve conduction

Box 1: Most common genetic causes of familial MND

| Gene mutation | Frequency | Proposed pathogenic mechanism | Evidence |
|---|------------------------|---|--------------------------|
| Hexanucleotide repeat expansion in gene C9ORF72 | 40% of familial cases | unknown | DeJesus-Hernandez et al. |
| Mutations in SOD1 gene | 20% of familial cases | Not fully understood, evidence for toxic gain of function | Rosen et al |
| Mutations in TDP-43 gene | 5% of familial cases | Role in RNA metabolism | Sreedharan et al |
| Mutations in FUS gene | 1-2% of familial cases | Role in RNA metabolism | Vance et al |

studies and needle electrode examination of muscles) is the most useful test in confirming a clinical diagnosis of ALS while MRI of the respective spinal segments helps to rule out any structural lesion which may be causing the EMG changes.

The progression of motor neuron disease is variable but average life expectancy is 2–3 years from symptom onset. About 10% of the patients live longer than 10 years. Respiratory failure resulting from weakness in respiratory muscles is the commonest cause for morbidity and mortality. Rarely, symptoms of respiratory failure such as shortness of breath, orthopnoea, sleep disturbances etc are the presenting feature of MND.

Aetiology and risk factors

MND is more commonly a sporadic disease, 5–10% of the cases have a family history. At least 12 different gene mutations have been identified in the families affected with MND (Box 1). Also, several “susceptibility” gene mutations

have been identified in sporadic cases which may act as genetic risk factors for developing the disease, when exposed to certain environmental/lifestyle risk factors. Putative lifestyle risk factors include extreme physical activity (which may be occupational or recreational), physical trauma (including electric shock), cigarette smoking and high dietary fat intake. However, many of the reported epidemiology studies are under powered, have poorly matched control groups and the results are often inconsistent and conflicting. Only smoking has been proven as a significant risk factor through evidence based approach. Male sex is an independent risk factor, a slightly higher incidence is observed in men (1.5:1).

Pathogenesis

The pathogenesis of neurodegeneration is complex and not fully understood. It has been proposed that multiple pathogenic processes may act together and culminate in the

common outcome as motor neuron degeneration. The molecular mechanisms of neurodegeneration and the evidence in their support are summarised below.

Oxidative stress

The mutations in SOD 1 gene (which encodes a major anti-oxidant protein) as established cause of familial MND and evidence of abnormal free radical metabolism in patients with MND supports the concept that oxidative stress contributes to motor neuron injury in MND. Anti-oxidants such as vitamin C and E are commonly prescribed to the MND patients although evidence from well designed clinical trials is lacking.³

Mitochondrial damage and dysfunction

Observations in this context include abnormal mitochondrial morphology and increased mitochondrial volume and abnormal mitochondrial calcium levels within motor neurons in sporadic MND.⁴ Also, reduced activity of complex IV of the mitochondrial respiratory chain

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The maximum dose regimen is 50 mg daily. For post-myocardial infarction heart failure patients eplerenone therapy should usually be started within 3-14 days after an acute myocardial infarction. For chronic heart failure NYHA class II patients, treatment should be initiated at a dose of 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks; taking into account the serum potassium level. Patients with a serum potassium of $>$ 5.0 mmol/L should not be started on eplerenone therapy. If serum potassium fluctuates after initiation, dose adjustment may be necessary. Periodic monitoring of serum potassium is recommended, particularly in the elderly, in patients with diabetes and in patients with renal impairment. Patients with moderate renal impairment (CrCl 30-60ml/min) should be started at 25mg every other day and the dose should be adjusted based on the potassium level. Frequent and regular monitoring of serum potassium is recommended in patients with mild-moderate hepatic impairment. **Use in children:** Not recommended. **Contra-indications:** Hypersensitivity to eplerenone or any of the excipients. Patients with serum potassium level $>$ 5.0 mmol/L at initiation. Severe renal insufficiency (eGFR $<$ 30 mL per minute per 1.73 m²). Severe hepatic insufficiency (Child Pugh Class C). Patients receiving potassium-sparing diuretics, potassium supplements or strong CYP3A4 inhibitors. The combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) with eplerenone. **Special Precautions:** Consistent with the mechanism of action, hyperkalaemia may occur with eplerenone. Serum potassium levels should be monitored in all patients at initiation of treatment and with a change in dosage. 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Care should also be taken when co-administering digoxin, warfarin, CYP3A4 inhibitors (e.g. verapamil, diltiazem, amiodarone) and CYP3A4 inducers. **Driving/Use of Machinery:** No studies have been performed, but it should be taken into account that dizziness may occur during treatment. **Use during pregnancy:** Caution should be exercised when prescribing eplerenone to pregnant women. **Lactation:** It is unknown if eplerenone is excreted in human breast milk. Because of the unknown potential for adverse effects on the breast fed infant, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. **Side-Effects:** *Common:* Hyperkalaemia, infection, dizziness, syncope, myocardial infarction, hypotension, cough, diarrhoea, nausea, constipation, renal impairment, rash, pruritus, muscle spasms, musculoskeletal pain, blood urea increased. *Uncommon:* Pyelonephritis, pharyngitis, eosinophilia, hypothyroidism, dehydration, hypercholesterolaemia, hypertriglyceridaemia, hyponatraemia, insomnia, headache, hypoaesthesia, atrial fibrillation, left ventricular failure, tachycardia, arterial thrombosis limb, orthostatic hypotension, flatulence, vomiting, hyperhidrosis, back pain, cholecystitis, asthenia, malaise, blood creatinine increased, epidermal growth factor receptor decreased, blood glucose increased, pyelonephritis, Gynaecomastia. *Not known:* Angioedema. 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is reported in sporadic MND.⁵ Mitochondrial DNA mutations have been identified in MND patients.⁶

Excitotoxicity

Overstimulation of post-synaptic glutamate receptors with excessive glutamate results in premature death of neurons by deranging intracellular calcium homeostasis and production of free radicals. This theory is supported by the fact that Riluzole (only licensed treatment for MND), inhibits glutamate release at the nerve terminals.⁷

Impaired axonal transport

Neuronal axons have a transport mechanism (axoplasmic transport) which allows trafficking of cargos between the cell bodies and nerve terminals. Impaired axonal transport may cause an energy deficit in the distal axon and recent evidence suggests that the neuromuscular junction and distal axonal compartment are affected early in the disease pathology.⁸

Apoptosis

Significantly increased activity of caspases 1 and 3 (key pro-apoptotic proteins) has been reported in the spinal cord of symptomatic SOD1 transgenic mice and deceased patients.⁹ Over expression of Bcl-2, a protein that inhibits apoptosis has been shown to delay the onset of motor neuron disease in mice models.¹⁰

Inflammation

Proinflammatory cytokines such as MCP-1, COX-2, TNF α and interleukins have been found to be elevated in CSF of patients with MND and hence an inflammatory process has been suggested in the pathogenesis of MND.¹¹⁻¹³ However, clinical trials evaluating the use of inflammatory modulators have not shown promising results.

Glial activation

Activated glial cells release pro-inflammatory cytokines which may cause damage to the motor neurons. Minocycline inhibits glial activation and has been shown to slow disease process in mutant SOD1 mice. However, a US trial in humans has been unsuccessful.¹⁴

Role of non-neuronal supporting cells

Astrocytes may contribute to the excitotoxic damage to the motor neurons by down regulating glutamate reuptake transporter EAAT2 receptor or actively releasing the excitatory neurotransmitter. Also, reactive

Box 2: Prognostic factors at diagnosis

| Parameter | Good prognostic factor | Poor prognostic factor |
|---|------------------------------------|--------------------------|
| Age of onset ¹⁵ | Juvenile onset (< 55 yrs) | Late onset (> 55 yrs) |
| Gender ¹⁶ | Male | Female |
| Time from symptom onset and diagnosis ¹⁷ | > 1 year | < 1 year |
| Site of onset ¹⁸ | Limb onset | Bulbar onset |
| Form of Disease ¹⁵ | PLS/PMA/flail arm-leg | ALS/PBP |
| Respiratory function at diagnosis ¹⁹ | *FVC > 75% | FVC < 75% |
| Weight ²⁰ | Maintaining weight | Rapid weight loss |
| Bulbar function ¹⁶ | Mild to moderate bulbar impairment | Severe bulbar impairment |
| Mental health ²¹ | Positive attitude | Depression |

* FVC – forced vital capacity, a measure of respiratory function

astrocytes secrete inflammatory mediators (prostaglandin E₂, leukotriene B₄, and nitric oxide) and release pro-apoptotic proteins which may trigger apoptosis in motor neurons.

Defective RNA processing

Mutation in the genes encoding for Fusion in Sarcoma (FUS) and TDP-43 are linked to familial MND. FUS and TDP-43 are involved in RNA processing pathways. Defects in RNA processing and defective interaction between specific RNAs and RNA binding proteins in the cytoplasm may result in degeneration of motor neurones.^{22,23}

Prognostic factors at diagnosis

The prognostic factors at the time of diagnosis are summarised in Box 2.

Indices of disease progression of MND

The following clinical parameters are used as the markers of disease progression. They are used to inform prognosis and to plan supportive interventions. Rapid declines in these parameters indicate an aggressive disease and a worse prognosis.

- Weight loss
- Functional decline (commonly monitored with ALS functional rating scale)
- Declining muscle scores (evaluated by manual muscle testing)
- Decline in forced vital capacity (FVC) or other respiratory parameters.

Management strategies

The management of motor neuron disease is challenging and requires a multidisciplinary approach. There

is no cure or treatment which may reverse weakness or arrest progression and hence emphasis is on control of symptoms through various modalities. There is evidence that good symptomatic care improves longevity and maintains quality of life. Ideally all care should be provided at or close to the patient's home in a co-ordinated fashion, with good communication between the hospital and the community services.

Pharmacological interventions

Disease modifying agents

Riluzole (Rilutek®) is the only disease modifying drug successfully tested in a placebo controlled trial.²⁴ However, it improves survival by an average of only 2–3 months. Its use is restricted to ALS form of MND as per NICE guidelines. Several other medicinal products have been tested without encouraging results. Anti-oxidants are commonly prescribed on theoretical grounds although evidence from human trials is lacking.

Symptomatic therapies

Pain

Pain in the limbs is a common complaint. Patients may have muscle pain (due to stiffness, spasticity or cramps), articular pain (due to immobility) or myofascial pain. Nature of the pain should be carefully assessed to select the appropriate remedy. Quinine sulphate is very effective for muscle cramps. Excessive muscle stiffness or spasticity may be helped with muscle relaxants (eg. baclofen). Gabapentin may be tried for myofascial pain. Physiotherapy, massage and regular re-positioning of the limbs should be combined with pharmacological measures.

Fatigue/asthenia

Fatigue may be a direct symptom of the disease process. Patients should be carefully assessed for a secondary cause such as depression, nutritional insufficiency, respiratory failure or poor sleep.

Emotional lability

Patients with predominantly upper motor neuron disease often have exaggerated emotional reflexes ie. uncontrollable crying or laughing. Anti-depressants like citalopram and amitriptyline are usually effective at controlling emotional lability.

Hypersialorrhea

Drooling of saliva is a representation of failing swallowing mechanism. Production of saliva can be suppressed with anticholinergic drugs (eg, hyoscine transdermal patch, atropine) or botulinum toxin injection into the salivary glands. A portable suction device may be required in extreme cases. Good oral hygiene should

be encouraged as suppression of saliva and poor oral hygiene may encourage oral thrush.

Thick sputum

Weakness in respiratory and or bulbar muscles may impair the cough reflex and hence patients may complain of an inability to expectorate. Use of anticholinergics to control saliva may contribute to the crusting of sputum. Mucolytics like carbocysteine or saline nebuliser are helpful to reduce the viscosity of sputum. Patients should be encouraged to maintain adequate hydration.

Dyspnoea

Dyspnoea or orthopnoea may be a frightening symptom and may induce considerable anxiety. It usually indicates significant respiratory muscle weakness but other causes such as a pulmonary embolism or chest infection should be considered. Non-invasive ventilatory support is effective in relieving dyspnoea. Morphine and benzodiazepines may be required to control dyspnoea and associated anxiety in the terminal stages of the disease.

Urinary urgency

Detrusor overactivity is a common symptom in patients with upper motor neuron disease. Antimuscarinic drugs such as oxybutynin, tolterodine or solifenacin are commonly used to reduce involuntary detrusor contractions.

Constipation

Patients with MND are prone to constipation due to lack of activity, dietary consistency changes and weak respiratory muscles (cannot generate sufficient intra-abdominal

pressure). Oral laxatives may not be sufficient and measures like enema or manual evacuation may be required.

Non-pharmacological interventions

Mobility aids

Simple orthotics such as foot-up splints may help improve mobility in the early stages of the disease. A community physiotherapist has an invaluable role in the continued assessment and provision of mobility aids eg. walking stick, Zimmer frame or wheelchair. Electronic wheelchair or mobility scooter may greatly enhance independence in patients with reasonable upper limb function. Occupational therapists have essential role in assessing a patient at his residence and offer adaptive measures like stair lift, wet room or clos-o-mat shower toilets. Much can be done to improve the quality of life, however funding is often a limiting factor.

Communication aids

The majority of the patients will eventually develop speech impairment. Modern communication devices are available for patients with dysphasia such as light writer or say-it-Sam tablet. Patients with no functional hand movement may use a head or foot mouse. In late stages, patients may be able to communicate with eye movements and picture charts only.

Nutritional support

MND patients are prone to malnutrition through a variety of reasons including dysphagia, fear of aspiration, difficulty in feeding and preparing meals and MND

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Drug Interactions: Concomitant use of other antimuscarinics and medicinal products with anticholinergic properties or with strong inhibitors of CYP3A4, may lead to more pronounced therapeutic and side-effects. Induction of CYP3A4 may lead to subtherapeutic plasma levels. Concomitant use with CYP3A4 inducers is not recommended. Co-administration of Toviaz with potent CYP2D6 inhibitors may lead to increased exposure and adverse events. A dose reduction to 4mg may be required. Fesoterodine may reduce the effect of products that stimulate the motility of the gastro-intestinal tract. **Pregnancy & Lactation:** Not recommended. See Full Prescribing Information. **Side Effects:** In clinical trials, the most commonly reported adverse reaction was dry mouth. Common reported events include dizziness, headache, dry eye, dry throat, abdominal pain, diarrhoea, dyspepsia, constipation, nausea, dysuria, insomnia. Other side-effects include uncommon; tachycardia, palpitations, somnolence, blurred vision, vertigo, urinary retention (including feeling of residual urine), ALT increased, GGT increased; rare angioedema, confusional state. Refer to SmPC for information on other side effects. **Driving and operating machinery:** The ability to drive and use machines may be affected by blurred vision, dizziness and somnolence, see side effects. **Overdose:** Treat with gastric lavage and give activated charcoal. Treat symptomatically. **Legal Category:** POM.

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being a hyper catabolic state. Help of a dietician and speech and language therapist is invaluable in advising about calorie intake, nutritional supplements, consistency of food and special swallowing techniques.

Enteral feeding is considered if significant symptoms of dysphagia eg. prolonged meal times, unable to finish meals due to fatigue or when body weight falls by more than 10% of the baseline weight as a result of swallowing difficulties. Though not proven by randomised controlled trials, there is clinical consensus that enteral feeding improves quality of life and survival in carefully selected patients. Both the American Academy of Neurologists and the European Federation of Neurological Societies recommend gastrostomy feeding for MND patients with significant dysphagia, to maintain adequate nutritional status.^{25, 26}

Respiratory support

MND can affect respiratory muscles and patients may develop respiratory failure at variable time points in their disease trajectory. Regular assessment of respiratory function is important to plan timely intervention. Respiratory support is usually provided by non-invasive positive pressure ventilation (NIPPV) via a face or nasal mask interface. It has been proven in a randomised controlled trial that treatment with NIV enhances survival by an average of seven months,²⁷ which is far above the survival benefit offered by the only licensed neuroprotective therapy.

Support with NIV should be combined with chest physiotherapy and cough augmentation techniques such as CoughAssist® or breath-stacking device. Periodic chest expansion is important to prevent basal atelectasis and stiffening of costochondral joints, thus preserving lung compliance. Poor airway clearance due to cough impairment carries the risk of potentially fatal respiratory tract infections. Patients should receive annual pneumococcal and influenza vaccines and avoid contacts with people with cold.

Palliative care

Patients should be linked into a palliative care team. There is substantial evidence that palliative care interventions improve quality of life for both patients and carers.²⁸ Hospice referral is particularly important for patients with significant respiratory impairment who are intolerant to NIV. With good palliative care and support of family, the majority of deaths from MND can be peaceful. Opiates, benzodiazepines and oxygen are the most commonly used palliative care measures. Morphine, midazolam and glycopyrrolate may be given as a continuous infusion by syringe driver to maximise symptom control. Death generally occurs in sleep from hypercapnic coma.

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Care for the carer

Carers have a central role in the overall day-to-day management of a patient with MND. Their well being and quality of life may be affected by the demands placed upon them. Sub-clinical depression is common amongst carers and should be recognised.

Role of Motor Neuron Disease Association (MNDA)

MNDA is a national charity in the UK working specifically for this disease. The association offers a range of services including information and advice, education and training sessions, equipments for loan and funding for MND research projects. It employs Regional Care Development Advisers who have detailed knowledge on the care and management of MND and work closely with local statutory services and community care providers to ensure effective support for the people affected by MND.

Conflict of interest: none

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