

# Motor Neuron Disease

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## 1. Introduction

Neurologists in the 19<sup>th</sup> century recognized 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 neurons degenerate. Furthermore, it was observed that there are forms of motor neuron degeneration which selectively affect upper motor neurons or lower motor neurons. A combination of upper and lower motor neuron dysfunction was named amyotrophic lateral sclerosis (ALS) by Charcot and Joffroy (Ringel, et al 1993). Jean-Martin Charcot first characterized the disease in 1874, naming the illness Amyotrophic lateral sclerosis (ALS) (Swash, 2001). In 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 neuron involvement (Ringel, et al 1993). ALS is now a term which classifies the most common form of the illness and is often used synonymously with MND (Swash, 2001). In the UK the umbrella term motor neuron disease (MND) is more common. MND is a disease of middle to late life with a mean age of onset of 58 years, (Ringel, et al 1993).

Actually, motor neuron diseases (MND) are a group of degenerative disorders that selectively affect motor neurons in the brain and spinal cord. Two groups of motor neurons are involved, lower motor neurons located in ventral horns of the spinal cord and brainstem motor nuclei, and upper motor neurons located in the cerebral cortex together with pyramidal tracts in spinal cord. The term MND is a broad spectrum term including amyotrophic lateral sclerosis.

## 2. Definitions and terminology of motor neuron disease (MND)

MND is a group of incurable progressive neurodegenerative disorders in which degeneration involves upper and lower motor neurons in different body regions, resulting in progressive weakness of bulbar, limbs and respiratory musculature, in different combination.

MND is an adult onset neurodegenerative disease which leads inexorably via weakness of limb, bulbar and respiratory muscles to death from respiratory failure three to five years later. (Allum and Shaw 2010).

## 3. Epidemiology of motor neuron disease

The prevalence of MND is 4-6 per 100,000 in most parts of the world, except the Western Pacific foci, (Leigh, 1991). However, its annual incidence is between 1.5 and 2/100,000 and

males are more commonly affected than females (1.4:1). The incidence increases with age with a mean age of onset of 63 years, (Ringel, et al 1993). It ranks as the third most common neurological degenerative disorder after Alzheimer's and Parkinson's disease (Talbot 2002).

In Guam, the incidence of MND has fallen from 87/100,000 in 1962 to 5/100,000 in 1985, (Rodgers-Johanson, et al. 1986).

Within the Caucasian population of Europe and North America, where most of the studies have been conducted, the lowest reported incidence of MND was 0.6 per 100,000 person – years in Italy, (De Domenice, et al. 1988) and the highest reported was 2.4 per 100,000 person-years in Finland (Murros and Fogelholm.1983). However, a lower incidence rate of 0.3/100,000 person-years was reported among Asian population, in China, (Fong, et al. 1996).

In the only well-conducted study of MND incidence among black African population, the incidence of MND was noted to be 0.9 per 100,000 person-years in Libya, (Radhakrishnan, et al. 1986).

The incidence of MND is said to be increasing, but this is probably the result of improved diagnosis, better awareness of the disease and an aging population, (Leigh and Ray-Chaudhuri.1994). The incidence increases after the age of 40 years, peaks in the late 60s and early 70s, and declines rapidly after that, (Logroscino, et al. 2008).

#### **4. Aetiology, pathology and pathogenesis of motor neuron disease**

MND is one of the complex and misunderstood diseases that health care professionals may encounter for various different reasons: (1) there are multiple different forms of the disease (Strong and Rosenfeld.2003), (2) the pathogenesis is not fully delineated (Wijesekera and Leigh.2009), (3) diagnosis can occur only by exclusion, (4) there exists only FDA approved medication, riluzole, for the treatment of ALS<sup>2</sup> (Washington.2007), and despite this, (5) there is no cure for this disease.

Environmental exposures during the Gulf war have been proposed as the explanation for an increased incidence of ALS among Gulf War veterans (Haley 2003, Horner et al, 2003).

##### **4.1 Neuropathological findings in MND**

Gross changes were frontotemporal atrophy, which was usually mild to moderate, neither circumscribed nor of a 'Knife-blade' type, and atrophy of the anterior roots in the cervicothoracic spinal cord, which was seen in cases with definite lower motor neuron involvement. Cortical atrophy was marked in the limbic system including the temporal pole, parahippocampus and amygdala but usually spared the hippocampus in typical ALS – Dementia (ALS-D) cases. (Yoshida 2004).

Histological changes included neuronal loss and gliosis with sponginess in layers II and III of frontotemporal cortices with predominant involvement of the limbic system including the anterior cingulate gyrus, anterior temporal and insular lobes, parahippocampus, subiculum and amygdala in typical cases. (Yoshida 2004).

The full pathogenesis of ALS is not well understood as it has not been fully elucidated by medical research. However, several key factors can be noted including: (1) Genetics, (2)

Excitotoxicity, (3) Oxidative stress, (4) Mitochondrial dysfunction, (5) Impaired axonal transport, (6) Neurofilament aggregation, (7) Protein aggregation, (8) Inflammatory dysfunction and contribution of non-neuronal cells, (9) Deficits of neurotrophic factors and dysfunction of signaling pathways, and (10) Apoptosis, (Wijesekera and Leigh.2009 and Shaw. 2005).

#### **4.2 Genetics**

Up to 90% of all ALS cases, occurs without family history, (sporadic ALS) and about 10% of cases are familial ALS (FALS). SALS is clinically indistinguishable from FALS, but the average age of onset in FALS is somewhat earlier, (Celveland and Rothstein (2001). Enteroviral infections and mutations of superoxide dismutase 1gene (SOD1) have been implicated in the pathogenesis of MND (oluwale et al 2001). About 25% of ALS cases, (Celveland and Rothstein (2001), and 2% of the sporadic cases, are linked to mutations in the gene encoding copper/zinc superoxide dismutase (SOD1). It is Known that there may be as many as six gene loci that code for the ALS phenotype, but only three have been identified. Several other mutations have also been documented to possibly take part in the pathogenesis of ALS, (Wijesekera and Leigh, 2009). Since the link between SOD1 and FALS was first established, >90 FALS-linked SOD1 mutations have been discovered, (Celveland and Rothstein (2001). Most of these mutations are point missense mutations, (Anderson, et al. 2003). Most of the genetics are transmitted via the autosomal dominant route, though some are autosomal recessive and others may be sex-linked, (Wijesekera and Leigh.2009).

#### **4.3 Excitotoxicity**

Excitotoxicity is a term used to signify the damage that occurs to neuronal cells that are characterized by overstimulated glutamate receptors, as glutamate is the major excitatory neurotransmitter in the human central nervous system (Riluzol monograph. 2011). As SOD1 codes for the major reuptake protein of glutamate, a mutation limits the concentration levels of that reuptake protein, allowing an excessive amount of glutamate to be present in the neuronal synapse. It is also postulated that glutamatergic toxicity plays a direct role in the destruction of neuronal cells in patients with ALS.( Shaw. 2005).

#### **4.4 Oxidative stress**

Oxidative stress is of particular interest to researchers due to the fact that the SOD1 gene mutation that is known to cause ALS, normally codes for an anti-oxidant protein. (Riluzol momgraph. 2011)

#### **4.5 Mitochondrial dysfunction**

There are many new data which supports the theory that mitochondrial dysfunction plays an important role in the pathogenesis of ALS. Multiple cases of dysfunctional mitochondria have been noted in post-mortem analyses of ALS patients. (Wijesekera and Leigh.2009) Dysfunctional mitochondria have also been linked to the SOD1 gene mutation in mice models. (Shaw. 2005)

#### **4.6 Impaired axonal transport**

The theory that axonal transport is a key to ALS pathogenesis stems from SOD1 transgenic mice models. Mice from these models often show slowed anterograde and retrograde axonal transport. Although no human ALS patient has presented with this problem, yet it is known to occur in several other neuromuscular disorders of the human body. (Wijesekera and Leigh.2009)

#### **4.7 Neurofilament aggregation**

Abnormal neuronal assembly, including accumulation of neurofilaments, are often seen in ALS patients. Neurofilaments can combine with a toxic form of peripherin, an intermediate filament protein, and become toxic to neurons even at modest concentration levels. This combination has been found in the spinal cord of ALS patients and not in controls. This evidence points to neurofilament aggregation as being a part of ALS pathogenesis. (Wijesekera and Leigh.2009)

#### **4.8 Protein aggregation**

Long debates as to whether protein aggregation take a part in disease pathogenesis have been occurred. It is possible that these inclusions may simply be innocent bystanders, or even beneficial to the cells. (Wijesekera and Leigh.2009)

#### **4.9 Inflammatory dysfunction and contribution of non-neuronal cells**

It has been recently discovered that SOD1 mutations alone are insufficient to cause ALS in transgenic mice, making the case that non-neuronal cells, as microglial and dendritic cells, may play a part in ALS pathogenesis (Shaw, 2005). ALS patients commonly experience activation of the non-neuronal microglial and dendritic cells. This activation has been shown to produce inflammatory cytokines such as interleukins and tumor necrosis factor (TNF). However, recent trials have yet to see success in utilizing immunomodulatory drug therapies to curve the progression of ALS. (Wijesekera and Leigh.2009).

#### **4.10 Deficits of neurotrophic factors and dysfunction of signaling pathways**

Lowered levels of neurotrophic factors have been noticed in post-mortem analysis of several ALS patients. In addition, three mutations in the Vascular Endothelial Growth Factors (VEGF) gene were thought to be associated with an increased risk for developing ALS. However, recently these finding have come under scrutiny due to an inability to replicate research results. (Wijesekera and Leigh.2009)

#### **4.11 Apoptosis**

Current research also skews towards examining if ALS motor neuron destruction occurs via a programmed cell death, or apoptosis. Several studies have shown that cell death due to ALS often occurs because of this programmed apoptosis, yet these findings are still being reviewed and discussed heavily. (Shaw. 2005).

## 5. Clinical presentation of motor neurone disease

Dilemmas of symptoms and signs are described for diagnosis of MND and its subtypes. Motor symptoms of both upper and lower motor neuron dysfunction can occur in any muscle group, including limbs, and, or bulbar regions. Combinations of the previous motor symptoms is not characteristic for MND and can be observed in many diseases, known as "MND Mimic Disorders" such as, Kennedy's diseases, multifocal motor neuropathy, brainstem lesions (syrinx, stroke,..... etc)

Meticulous evaluation by thorough history and examination by two or more specialists of neurology are required for diagnosis of MND. Special investigations are required for diagnosis of MND and differentiation from MND mimics.

Preclinical stage	Diagnosis stage	Progression stage	Terminal stage
<ul style="list-style-type: none"> <li>• Long duration (months or even years)</li> <li>• Disease spread through motor system</li> <li>• Usually Asymptomatic</li> </ul>	<ul style="list-style-type: none"> <li>• Selective involvement of motor neurons in the anterior horns of the spinal cord early and late in the disease (Swash et al. 1986)</li> <li>• corticospinal pathways in the cord are similarly, asymmetrically affected (Ingram and Swash 1987)</li> <li>• Onuf's sacral nucleus (innervate anal and urinary sphincter muscles) are always spared (Schroder, and Reske Nelson 1984)</li> <li>• Ocular motor nuclei are also relatively resistant (Mulder 1982)</li> </ul>	<ul style="list-style-type: none"> <li>• weakness of one leg followed by other leg and patient will require a wheelchair to assist him</li> <li>• Swallowing Problems</li> <li>• Respiratory muscle weakness and dyspnea</li> <li>• All these symptoms are observed in different combinations according to different subtypes of MND</li> </ul>	<ul style="list-style-type: none"> <li>• Respiratory insufficiency symptoms orthopnea, excessive daytime sleepiness, poor concentration, memory and appetite and signs of tachypnea, tachycardia, syncope and confusion, (Radunovic et al 2007.)</li> <li>• Nursed and care for 24 hours</li> <li>• Medication, Diet, Hygiene and special attention for respiration.</li> </ul>

Table 1. Stages of Motor Neuron Disease (MND)

## 6. Bad prognostic factors for MND

1. Late age of onset.
2. Severe and early presentations of bulbar symptoms.
3. Respiratory complications.

The classical concept that MND only affects the motor system is obsolete. MND is considered to be a multisystem neurodegenerative disease. There is increasing clinical evidence for autonomic dysfunction (Baltadzhieva, et al 2006 and Takeda, et al, 1994), sensory abnormalities (Takeda et al, 1994) (Pugdahl et al, 2007) and ophthalmoplegia

(Takeda, et al, 1994) in MND. On the other hand, there are good pathological accounts of the involvement of sympathetic and parasympathetic neurons, (Takeda, et al, 1994), Onuf's nucleus (which innervates the pelvic floor sphincteric muscles), (Takeda, et al, 1994) peripheral sensory nerves, (Isaacs, et al. 2007) and oculomotor nuclei. (Takeda, et al, 1994). However, in practical terms, the presence of prominent ophthalmoplegia, sensory signs or sphincter dysfunction should raise doubts regarding the diagnosis of MND, unless there are a clear alternative explanation. Death usually results from ventilatory muscle weakness causing respiratory failure.

## 7. Motor neuron disease presenting to non neurological specialists

**Respiratory:** Progressive respiratory Failure

**Ear, nose, and throat:** Dysphagia.

**Orthopaedics/ neurosurgery:** Foot drop or other symptoms suggestive of compressive radiculopathy

**Elderly care:** Difficulty walking. (Talbot 2002).

	ALS	PMA	PLS	PBP
1. Age of onset	50-70 years		40 - 60 years	
2. Percent of Frequency (Leigh et al 2003)	60 - 70 %	10 %	1 %	20%
3. Incidence (Strong and Rosenfeld, 2003)	1,2-1,8/100,000	-----	1/1000,000-Brugman and wokkle 2004	-----
4. Prevalence (van der, Graaff, 2004)	5-9/100,000	-----	10-20/1000,000-Brugman and wokkle 2004	-----
5. Male to female Ratio ( Leigh et al 2003)	3:2	3:4	3:1 (Talbot 2002)	1:1
6. Anatomical localization	Cortical & spinal	spinal cord	Limb, Bulbar (Pseudo bulbar)	Bulbar, Speech and limb
7. Upper Motor Neuron manifestations	Present	Absent	Present	Absent
8. Lower Motor Neuron manifestation	Present	Present in Limb muscles	absent	Present in bulbar muscles
9. Cognitive impairment	Present and some group of ALS without cognitive impairment	Present	Usually absent (Raaphorst et al 2010)	Absent

10. Bulbar symptoms	Present	Absent	Present	Prominent
11. Mimic syndromes	-Compressive myeloradiculopathy, -Paraneoplastic syndrome, -Encephalo-myelitis with anterior horn cell involvement	-Inflammatory Myopathy -Multifocal motor neuropathy with conduction block -Myasthenia Gravis -Toxic Neuropathies -Post polio Progressive muscular atrophy	-Primary progressive multiple sclerosis, -vit. B12 deficiency -Hereditary spastic Paraparesis, -Rarely small vessel cerebrovascular diseases -cervical Spondylotic myelopathy	Posterior inferior cerebellar artery occlusion
12. Emotional lability	May be Present	Present	Prominent	Absent
13. Investigations a. EMG&CV	Positive- lower motor neuron manifestations	Positive- lower motor neuron manifestations	Normal	Fibrillation and Positive sharp waves.
b. MRI brain When Bulbar manifestations are isolated symptoms and signs	Normal	Normal	Normal	Normal
c. MRI spinal cord All Limb onset without bulbar symptoms	Normal	----	Normal	----
14. Prognosis Median Survival (Leigh et al 2003)	3-4 years	5 years, more long survivors (>10 years)	20 years and More	2-3years

Table 2. Clinical Subtypes of Motor Neuron Disease

## 8. Cognitive function impairment in motor neuron disease

Cognitive impairment is increasingly being recognized in MND. Subtle subclinical cognitive defects and frontal lobe dysfunction may be demonstrated in up to half of MND patients with detailed neuropsychological testing (Ringholz, et al. 2005). Several genetic mutations of MND have been identified in association with frontotemporal dementia and/or parkinsonism (Valdmanis and Rouleau. 2008). It is well recognized that MND is a multisystem disorder (Geser, et al, 2008) with compromise of regions beyond the motor

system, including cortical areas which are consistently involved in FTD. It comes as no surprise, therefore, that a proportion of patients presenting with MND manifest cognitive and/or behavioural changes which may be severe enough in some instances to reach criteria for frank FTD.(Irwin, et al, 2007).

### 8.1 Amyotrophic lateral sclerosis and frontotemporal dementia (ALS-FTD)

There is increasing clinical, imaging and neurophysiological evidence that ALS represents a multisystem neurodegenerative disease. Neurodegeneration is not restricted to motor neurons, but also includes parts of the brain other than the motor cortex, especially the prefrontal and/or anterior temporal lobe, that contribute to the clinical syndrome. In some cases an evident dementia that resembles frontotemporal degeneration (FTD) was observed. It is now suggested that ALS and FTD are closely related conditions with overlapping clinical, pathological, radiological, and genetic characteristics. The presence of a frontal dementia in ALS has also crucial practical consequences for management of the patients, whose disorder requires critical life decisions for enteral nutrition and respiratory complications. (Zago, et al. 2010).

### 8.2 The new classification of cognitive and behavioral disorder in ALS

In 2009, Strong and colleagues articulated new guidelines to direct ongoing investigations of cognitive and behavioral syndromes in ALS (Strong et al., 2009). To define the

Domain	Test
<b>Executive measure</b>	Wisconsin Card Sorting Test, Controlled Oral Word Association, FAS, D Words, Animal fluency, Written Word Fluency Design Fluency, California Card Sorting Test, Stroop Colour-Word Interference Test, Trail Making Test
<b>Memory/Learning</b>	Rey Auditory Verbal Learning Test, California Verbal Learning Test II, Warrington Recognition Memory Test, Wechsler Logical Memory and Visual Reproduction, Wechsler Paired Associate Learning, Kndrik Object Learning Test
<b>Attention/Concentration</b>	Verbal Serial Attention Test, Consonant trigrams Test, Symbol Digit Modit Modality Test, Paced Auditory Serial Addition Task, Digit Span
<b>Language</b>	Boston Naming Test, Graded Naming Test, Pyramid and palm Trees, Peabody Picture Vocabulary Test, British Picture Vocabulary Test, Test for the Reception of grammar
<b>Visual/Spatial</b>	Judgement of line Orientation, Benton Facial Recognition Test, Block Design, Motor-Free Visual Perception Test-Revised, Visual Object and Space Perception Battery
<b>Emotional/ Behavioral functioning</b>	Neuropsychiatric inventory, frontal Behavioural Inventory, Frontal Systems Behavioural Scale

Table 3. Neuropsychological test for the evaluation of cognitive/behavioral impairment in ALS (modified from Strong et al. 2009), with permission.

neuropsychological status of ALS patients a framework was based on four different axes. Axis I is based on the EL Escorial criteria proposed in 1998, that includes possible, probable, and definite ALS clinical subtypes. This multidimensional approach incorporates several criteria (Brooks et al, 2000). The novelty of the classification lies primarily in Axis II with the proposal of five categories which classify ALS patients along a continuum: (1) ALS patients cognitively and behaviorally intact; (2) ALS patients with mild cognitive impairments; (3) ALS patients with mild behavioral impairment; (4) ALS with a full-fledged fronto-temporal dementia; (5) ALS with other non FTD-forms of dementia.

Axis III indicates the presence, in addition to frontotemporal impairments, of additional non-motoneuronal disease manifestations such as extrapyramidal signs, cerebellar degenerations, autonomic dysfunctions, sensory impairments, and ocular motility abnormalities. The absence of the above indicates a "pure form," while their presence defines "complicated forms" with additional pathological motor aspects. Axis IV, instead, provides the search for factors which could modify the course of the disease. Several disease modifiers have been reported in literature associated with longer survival, age at symptom onset (< 45 years), gender (male/sex), and site of the disease onset (bulbar or limb).

## 9. Language

Language deficits are occasionally found in the early stages of the disease. (Abrahams, et al. 2004).

The spectrum of language impairment in MND is wider than simply a problem in speech production due to dysarthria, but it is yet to be fully characterized. Reduced verbal output (adynamism) evolving into mutism has been reported, as well as echolalia. Perseverations, stereotypical expressions, (Bak and Hodges. 2004), true non-fluent aphasia with phonological and/or syntactic deficits and comprehension impairment have been reported in isolated cases. (Tsuchiya, et al. 2000)

MND has also been associated with apraxia of speech, in which there is breakdown in articulatory planning, producing slowed, effortful and dysprosodic speech with problems repeating multisyllabic words. Apraxia of speech is often accompanied by orobuccal apraxia but not necessarily with aphasia.(Duffy, et al ,2007).

## 10. Memory

It has been difficult to categorize the pattern of memory impairment, but current evidence suggests that memory problems are related to abnormalities in retrieval of the information secondary to frontal dysfunction. (Neary, et al. 2000). Memory problems involve primarily immediate recall, (Phukan. et al. 2007) but impairment of visual memory also has been implicated,(Kew, et al.1993)

Frontal, temporal and thalamic hypoperfusion on SPECT has been shown to correlate with the severity of memory impairment. (Montovan, et al. 2003).

Most strikingly, learning and memory were found to be significantly improved in patients in the later stages of the disease, (Lakerveld et al, 2008).

<b>Definite ALS</b>	Upper and lower motor neuron signs in at least three body regions (upper limb, lower limb, bulbar, thoracic).
<b>Clinically probable ALS</b>	Upper and lower motor neuron signs in at least two regions, with some upper motor neuron signs necessarily rostral to the lower motor neuron signs
<b>Clinically probable ALS: Laboratory-supported ALS</b>	Clinical signs of upper and lower motor neuron dysfunction in only one region, or when upper motor neuron signs alone are present in one region and lower motor neuron signs defined by electromyographic criteria are present in at least two limbs, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
<b>Clinically possible ALS</b>	Clinical signs of upper and lower motor neuron dysfunction are together in only one region, or upper motor neuron signs are found alone in two or more regions, or lower motor neuron signs are found rostral to upper motor neuron signs and the diagnosis of clinically probable: laboratory-supported ALS cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiological, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded

\* (Brooks, 1994 and Brooks, et al. 2000)

\*\* ALS: amyotrophic lateral sclerosis

Table 4. Revised El Escorial criteria for the diagnosis of ALS.\*

## **11. Diagnostic criteria for motor neuron disease (amyotrophic lateral sclerosis, ALS) by\*\* Leigh and Ray – Chaudhuri 1994**

The diagnosis of ALS requires the presence of:

- LMN signs (including EMG features in clinically normal muscles)
- UMN signs
- Progression of the disorder

### **11.1 Diagnostic categories**

- **Definite ALS:** UMN plus LMN signs in three regions\*\*
- **Probable ALS:** UMN plus LMN signs in two regions with UMN signs rostral to LMN signs
- **Possible ALS:** UMN plus LMN signs in one region, or UMN signs in two or three regions, such as in monomelic ALS, progressive bulbar palsy, and primary lateral sclerosis
- **Suspected ALS:** LMN signs in two or three regions, such as in progressive muscular atrophy, and other motor syndromes.

### 11.2 The diagnosis of ALS requires the absence of

- Sensory signs
- Sphincter disturbances
- Visual disturbances
- Autonomic dysfunction
- Parkinson's disease
- Alzheimer-type dementia
- ALS "mimic" syndromes

### 11.3 The diagnosis of ALS is supported by

- Fasciculation in one or more regions
- Neurogenic change in EMG studies
- Normal motor and sensory nerve conduction (distal motor latencies may be increased)
- Absence of conduction block

Regions are defined as follows: brainstem, brachial, thorax and trunk, crural. UMN= Upper motor neuron; LMN= lower motor neuron.

## 12. Management of motor neuron disease (MND)

### 12.1 Investigations

There are no specific investigations for MND. Till now there are no specific biochemical or pathological markers of MND. The aim of Electrophysiological, Imaging and laboratory investigations is to exclude MND mimics and/ or to support clinical signs presented by the patients.

Allum and Shaw (2010) clarified that investigations are important adjuncts to the clinical diagnosis of MND. Properly used they can provide supportive evidence of the clinical findings and help delineate the extent of disease. Investigations are also important to identify benign or treatable MND mimics.

### 12.2 Treatment plan of motor neuron disease

Although MND is still incurable disease up till now, in the last two decades MND management has evolved rapidly. Symptomatic treatment of MND still had the upper hand of management plan, especially for respiratory and bulbar complications. A team of work including neurologist, highly qualified nurses, ICU specialist in respiratory complications, psychologist, dietitian, physiotherapy and speech therapist must be involved for management plan and follow up of MND patients, table (5).

Thus treatment strategy of MND was aimed towards;

1. Delay Progression of the disease and prevent further loss of motor neurons especially in the early stage of the disease
2. Symptomatomatic treatment to alleviate symptoms of the disease aiming to maintain quality of life

Types of investigatory Tools	Aim	Findings
<b>I- Electrophysiology</b> <ul style="list-style-type: none"> <li>• Electromyography</li> </ul>	Identification of LMN loss help in diagnosis of ALS by establishing the Presence of subclinical LMN involvement (Eisen and Swash. 2001)	<ul style="list-style-type: none"> <li>• Active denervation (positive sharp waves, fibrillation potentials, Fasciculation Potentials)</li> <li>• Chronic denervation evidenced by large motor unit potentials (Allum and Shaw 2010)</li> </ul>
<ul style="list-style-type: none"> <li>• Single fibre EMG, macro EMG and central motor conduction using magnetic stimulation</li> </ul>	Reflect early reinnervation and collateral sprouting and may provide evidence of A.H.C. damage in normal muscles (Leigh Ray - chaudhuri 1994)	Abnormal Jitter and blocking of neuromuscular trans -mission (Leig Ray - chaudhuri 1994)
<b>Nerve conduction studies</b> <b>Motor conduction Velocity</b>	To exclude disorders that mimic ALS	<ul style="list-style-type: none"> <li>• Normal in early stages of ALS.</li> <li>• In advanced disease the compound muscle action potential amplitude becomes reduced, indicating denervation (Daube. 2000)</li> </ul>
<b>Sensory conduction velocity</b>	Differentiating ALS From demyelinating neuropathies (Eisen. 2001)	<ul style="list-style-type: none"> <li>• Typically normal</li> <li>• Abnormal SCV should raise suspicion of an alternative diagnosis (Eisen. 2001)</li> </ul>
<b>II-Imaging</b> <ul style="list-style-type: none"> <li>• MRI spine for Limb onset ALS without bulbar manifestation</li> </ul>	To exclude cord and root compression	Normal
<ul style="list-style-type: none"> <li>• MRI brain for ALS presented by bulbar manifestation</li> </ul>	To exclude infiltrative lesion of tongue and pharynx (Turner, et al, 2009)	Normal
<b>III- laboratory investigations</b> <ul style="list-style-type: none"> <li>• Routine investigations (complete blood count, liver, kidney and thyroid function tests, Blood sugar curve electrolyte, calcium, CK----- etc</li> </ul>	To exclude MND minics as <ul style="list-style-type: none"> <li>- Thyrotoxicosis</li> <li>- lymphomas</li> <li>- Paraneoplastic syndrome</li> <li>- Diabetic amyotrophy.</li> </ul>	According to diagnosed neurological disorders

Table 5. Investigatory Tools for MND

<b>Neurologist</b>	Diagnosis, disclosure of diagnosis, treatment and symptom management, initiation of respiratory and nutritional interventions, unbiased information regarding research developments
<b>Family Doctor</b>	Symptom control, drug monitoring, liaison with other teams
<b>ALS Specialist Nurse</b>	Liaison with medical team and coordination of care, home visits, practical advice regarding accessing support services, patient advocacy
<b>Speech &amp; Language Therapist</b>	Evaluation and monitoring of dysphagia and aspiration, speech therapy and counseling regarding communication devices
<b>Occupational Therapist</b>	Optimization of the patient's environment. Advice regarding safety awareness, adaptive and splinting devices, activity modification, driving, energy conservation, home modification
<b>Dietitian/Nutritionist</b>	Evaluation of nutritional status and the need for tube feeding, management of dysphagia, management of enteral feeding
<b>Physiotherapist</b>	Evaluation of muscle strength and function, advice regarding walking aids and orthoses, safety awareness
<b>Social Worker</b>	Advice and control, pain management, maintenance of quality of life, preservation of dignity
<b>Psychiatry and Neuropsychology</b>	Evaluation and management of cognitive impairment/dementia, adjustment disorders, anxiety and depression
<b>Respiratory Physician</b>	Assessment of respiratory dysfunction, initiation of non-invasive ventilation

\* (phukan and Hardiman, 2009)

Table 6. Roles of the multidisciplinary team\* with permission

### 12.3 Different types of treatment

1. pharmacological
2. symptomatic and
3. treatment of complications

#### 12.3.1 Pharmacological treatment

Riluzole (2-amino-6-(trifluoromethoxy) benzothiazole, RP 54274) is the only drug licensed to treat ALS. Although the drug reduces glutamate-induced excitotoxicity, its precise mechanism in ALS is unknown. A Cochrane Library meta-analysis (including three double-blind randomized placebo controlled trials by (Miller, 2002) suggests that riluzole provides a 9% gain in the probability of surviving one year and adds approximately 2 months to patient survival.

#### Riluzole, exerts the following pharmacologic effects:

- An inhibitory effect on glutamate release.
- Inactivation of Voltage – dependent sodium channels.
- Ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptor (Riluzole monograph 2011).

- **Dosage** 50mg twice daily
- **Side Effects** Nausea and vomiting, Asthenia, somnolence Headache, dizziness, and vertigo
- **Serious Adverse Effects**
  - Elevation in liver transaminases. Regular monitoring of liver function is advised (every month for 3 months, every 3 months for a further nine months then annually thereafter).
  - Rare cases of neutropenia have been reported. White cell count must be checked in the case of febrile illness

**Contraindications**-Renal and hepatic impairment Pregnancy and breast-feeding (Brockington and Shaw, 2003)

### 12.3.2 Symptomatic treatment

Symptom	Cause	Drugs	Other treatment
<b>Cramps</b>	Changes in motor function	Carbamazepine Phenyton Magnesium (Miller, et al, 1999; Andersen, et al, 2005)	Physiotherapy Physical exercise Massage Hydrotherapy (Miller, et al, 1999; Andersen, et al, 2005)
<b>Spasticity</b>	Corticospinal tract damage	Baclofen Tizanidine Dantrolene Botulinum toxin type A (Wnterholler et al,2002 ; Restivo et al, 2002)	Physiotherapy (Millul et al, 2005) Hydrotherapy Cryotherapy
<b>Excessive watery Saliva</b>	Bulbar weakness	Atropine Hyoscine hydrobromide (Miller, et al, 1999; Andersen, et al, 2005) Amitriptyline (Bradley et al, 2001)	Home suction device Nebulisation (Andersen, et al, 2005) injections of botulinum toxin into parotid glands (Giess et al, 2000/ Winterholler et al, 2001) irradiation of the salivary glands (Iannaccone et al, 1996; Stalpers and Moser, 2002)
<b>Persistent saliva and bronchial secretions</b>	-Bulbar weakness - Respiratory complications	Carbocisteine Propranolol Metoprolol (Newall, et al, 1996)	Home suction device hydrobromide (Miller, et al, 1999/ Andersen, et al, 2005) Reduced intake of diary products, alcohol, and caffeine.

<b>Excessive or violent yawning</b>	Corticospinal tract damage (pseudobulbar syndrome)	Baclofen	
<b>Laryngospasm</b>	Pharyngeal sensitivity	Lorazepam	Reassurance
<b>Pain</b>	Immobility, stiffness	- Simple analgesics - Non-steroidal anti-inflammatory drugs - Opioids	Comfort (seating, sleeping, day and night care)
<b>Emotional lability</b>	Pseudobulbar syndrome	Tricyclic antidepressant Selective serotonin-reuptake inhibitors (Iannaccone and Ferini, 1996) Levodopa Dextrometorphan and quinidien (Brooks, et al, 2004)	
<b>Communication difficulties</b>			Speaking techniques (Murphy, 2004) Voice amplifiers Brain-computer interfaces (Kübler et al, 2005)
<b>Constipation</b>	Immobility; opiates, Dehydration	Lactulose Senna	Hydration Increased fiber intake
<b>Depression</b>	- Hopelessness; - Inability to communicate; and frustration	Amitriptyline Citalopram	Psychological support counseling
<b>Insomnia</b>	Discomfort, pain, depression; (consider respiratory insufficiency)	Amitriptyline Zolpidem	Comfort, analgesia
<b>Anxiety</b>	Many Factors	- Lorazepam - Midazolam - Diazepam suppositories	Psychological support, counseling
<b>Fatigue</b>	- Muscle weakness - Anxiety - Depression		Modafinil (Bradly et al 2001)

Table 7. Symptomatic treatment of Motor Neuron Disease. Modified From Radunovic et al 2007 and Leigh et al 2003

### 12.3.3 Treatment of complication

#### a. Respiratory complications

Respiratory impairment is common in MND and may develop because of respiratory muscle weakness, impaired bulbar function causing aspiration or obstructive sleep apnea, or defects in central control. Dyspnea may be due to infection, pulmonary embolus, or airway obstruction from mucous plug or inhaled pharyngeal contents. (Howard and Wiles, 1989).

Symptoms of respiratory insufficiency may be subtle and develop insidiously. Patients may report dyspnea, orthopnea, sleep fragmentation due to hypoventilation, morning headaches, daytime somnolence and fatigue, poor concentration/memory and nocturia. Others may be asymptomatic. Respiratory muscle weakness is an independent predictor of quality of life. (Bourke, et al, 2001) and respiratory failure is the most common cause of death in ALS patients. Assessment of respiratory insufficiency includes history, physical examination, early morning arterial blood gas, and overnight pulse oximetry.

Nocturnal hypoventilation may present as daytime hypersomnolence, lethargy, morning headaches, poor concentration, depression, anxiety, and irritability, while obstructive sleep apnea is characterized by snoring and restless sleep with abnormal movements. (Howard and Orrell 2002).

#### Types of mechanical ventilation

There are several types of ventilatory aids. These are broadly classified in terms of invasive versus noninvasive.

As its name suggests, invasive techniques require an endotracheal tube or more commonly a tracheostomy. For patients in advanced respiratory failure (ie, no respiratory muscle function), invasive ventilators can assume complete control of ventilation. (Simonds. 2003).

Non-invasive ventilatory aids can be divided into two groups, negative or positive pressure ventilators. Negative pressure is exerted to the chest or abdominal wall mechanically to assist inspiration. Positive pressure devices can be set to deliver variable inspiratory and expiratory pressures, triggered by spontaneous effort (Simonds. 2003).

#### b. Management of Dysphagia

Management of Dysphagia includes modification of food and fluid consistency, postural advice (e.g. chin tuck: flexing the neck forward on swallowing to protect the airway), and parenteral feeding.

A percutaneous endoscopic gastrostomy (PEG) placement is indicated for those who have symptomatic dysphagia or significant weight loss. (Miller, et al. 2002). Patients and their families should be suitably counseled regarding the benefits and risks of the procedure.

### 13. Conclusion

Motor neuron disease is of the most common neurodegenerative disorders of unknown etiology, and had no specific treatment. ALS is the commonest type, and in most literatures is used as a synonym for motor neuron disease. Diagnosis is still clinical, mainly, and the investigatory tools have a definite role for diagnosis of other motor neuron mimics. Once motor neuron disease is diagnosed, the prognosis is usually bad, especially when bulbar, and respiratory complications are evident.

## 14. References

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