CHAPTER

# 88

# Motor Neuron Diseases

**Joy D Desai**

## NOMENCLATURE

Charcot used the term 'Amyotrophic Lateral Sclerosis' (ALS), a description based on clinical and neuropathological features in patients assessed by him and studied at autopsy.[1] Lord Brain in 1962 used the term Motor Neuron Disease to encompass entities constituting the other clinical manifestations: amyotrophic lateral sclerosis, progressive bulbar palsy, and progressive muscular atrophy.[2] Essentially, the two terms ALS and MND are currently considered synonymous and used to describe clinical entities derived from degeneration within the anterior horn cell and the pyramidal tracts to somatic and bulbar musculature with variable segmental involvement producing differing presentations in different patients.[3] The clinical phenotype varies according to the segmental dysfunction within these parts of the neuraxis, which occurs at the time of clinical presentation.

## AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic Lateral Sclerosis (ALS) is a progressive, relentless, degenerative disorder characterized by a pathological change restricted to the cortical Betz cells, pyramidal tracts, selective brainstem cranial nerve neurons, and the spinal anterior horn cells in variable permutations and combinations. The onset can vary in its topography within the nervous system determining the pattern of initial limb involvement and later its progression. The symptoms of lower motor neuron dysfunction are, weakness, cramps, incoordination and fatigue, while its physical signs are the presence of weakness, atrophy, fasciculations, hypotonia and suppression of deep tendon reflexes. The symptoms of upper motor neuron dysfunction are weakness, incoordination, stiffness and slowing, while the corresponding physical signs are the presence of spasticity, brisk deep tendon reflexes and abnormal reflexes especially the Babinski and Hoffman signs. Depending on the site of onset, the extent of involvement of the neuraxis in the disease process, and the stage of the disease, these symptoms and signs are present in varying combinations.

Practically, patients may present with symptoms of difficulty in arising from a chair, tiredness, tripping and inability to button and unbutton clothing, perceived cramps and twitching of muscles. Some may notice and change in speech due to dysarthria and difficulty in swallowing due to bulbar or pseudo-bulbar weakness producing frequent coughing at meal times. Family members may notice slurring of speech due to spastic dysarthria. With the passage of time the whole gamut of

symptoms and signs may progress variably. In patients in whom the respiratory muscles are affected by ALS, progressive dyspnoea on exertion and later at rest may also compound the clinical challenges. The usual course of progression in ALS is relentless with death occurring in 50% of patients by three to four years from onset.[4]

The absence of overt sensory, sphincter and oculomotor dysfunction serves to distinguish ALS from other disorders of the lower motor neuron.

A variable proportion of patients with ALS may develop personality and behavioural changes. Cognitive assessment reveals impairment in planning ability, execution of strategies and ability to perform complex sequential tasks occasionally associated with frontal lobe release signs.[5] Although dementia by the true definition is unusual in ALS, these features of impaired executive functioning, reflect involvement of the frontal lobes in the disease process.[6,7] Such frontal lobe dysfunction is more common in patients with predominantly bulbar type of ALS.[8]

Rarely, some patients exhibit parkinsonian features and loss of postural reflexes (resulting in retropulsion) in addition to the characteristic motor signs of ALS.[9,10]

Progressive bulbar palsy (PBP) is the nomenclature for a progressive disease presenting with bulbar dysfunction due to destruction of motor neurons in the brainstem. Sometimes this syndrome includes evidence of upper motor neuron dysfunction. Historically, it has been considered a 'bulbar' form of ALS/MND. Some patients with progressive bulbar dysfunction of this degenerative kind could evolve into ALS with progression of the disease resulting in limb involvement. Many succumb to aspiration secondary to the bulbar paralysis while clinically restricted to the bulbar dysfunction only. Understandably, this type of MND has a poorer prognosis than ALS. The clinical features of this phenotype of MND often blurs or evolves into ALS.

Progressive muscular atrophy (PMA) refers to motor neuron disease presenting with weakness and wasting of muscles of the limb, and trunk muscles without evidence of upper motor neuron dysfunction. This condition may mimic adult onset proximal spinal muscular atrophy (SMA). The more rapid progression, and the later development of brisk reflexes may assist in differentiating PMA from SMA, since in SMA the tendon reflexes are usually reduced, and the plantar responses are always flexor. The prognosis of this form of motor neuron disease

may be different from that of the classical ALS form of motor neuron disease.

Primary lateral sclerosis (PLS) typically presents with a slowly progressive spastic gait disorder. Over months or years, the upper limbs are involved and in some a pseudo-bulbar syndrome develops. Hyper-reflexia, and Babinski and Hoffman signs are characteristic features, while lower motor neuron signs and sphincter dysfunction are absent. The clinical course and survival are much longer than ALS of Charcot type.

Based on clinical, radiological and pathological studies[11, 12] diagnostic criteria have been laid down. PLS may be a paraneoplastic manifestation of breast carcinoma.[13] PLS is a very rare disorder.

## DIAGNOSTIC CRITERIA FOR ALS

The diagnosis of ALS is not difficult to make once a clinician is aware of the spectrum of symptoms and signs that constitute the condition. Challenges lie in identifying patients early when all features may not have evolved in a given patient. The current accepted criteria for designation of ALS as a diagnostic entity for research are known as the 'El Escorial' criteria. These criteria were proposed after a meeting at the San Lorenzo Monastery in El Escorial near Madrid, Spain by the World Federation of Neurology in May 1990. Understanding of the spectrum of manifestations has changed over the years resulting in proposals to revise these criteria both from the electrodiagnostic point of view and the clinical.

The following revised El Escorial criteria serve as a framework to broadly identify categories of patients clinically suspected to suffer from ALS or MND. Some of the original 1990 proposed criteria have been modified to accommodate current understanding ALS.[14]

## REVISED EL ESCORIAL CRITERIA FOR THE DIAGNOSIS OF ALS

### Clinically definite ALS

- Evidence of upper motor neuron plus lower motor neuron signs in the bulbar region and at least two spinal regions **or**

- The presence of upper motor neuron signs in two spinal regions and lower motor neuron signs in three spinal regions.

### Clinically probable ALS

- Evidence of upper motor neuron plus lower motor neuron signs in at least two spinal regions with some upper motor neuron signs rostral to lower motor neuron signs.

### Probable, Laboratory supported ALS

- Clinical evidence of upper motor neuron signs and lower motor neuron signs in only one region, or

- Upper motor neuron signs alone in one region, and lower motor neuron signs defined by EMG criteria in at least two muscles of different root and nerve origin in two limbs.

### Possible ALS

- Upper motor neuron plus lower motor neuron signs in one region only, or

- Upper motor neuron signs alone in two or more regions, or

- Lower motor neuron signs found rostral to upper motor neuron signs.

(Regions: bulbar, cervical, thoracic, and lumbosacral)

The differential diagnosis of ALS includes rare presentations due to paraneoplasia, the concordant occurrence of cervical and lumbar radiculopathy due to degenerative spinal disease, and occasionally multi-focal motor neuropathy. Most patients undergo routine haematology, biochemistry, endocrine evaluation, CSF examination, EMG/NCV studies, and MRI of the spine.

## THERAPY IN ALS

The therapy of ALS till recently was restricted to symptomatic management. However, on the basis of two clinical trials,[15, 16] the American FDA has approved Riluzole for the treatment of ALS. The first clinical trial of riluzole in ALS was a multi-centre, stratified, randomized, double-blinded, placebo-controlled study, the results of which were announced in early 1994.[15] The study involved 155 patients, of whom 77 were assigned to receive riluzole 100mg/day and 78 placebo. The patients entered in this study were stratified and balanced according to the centre and the type of onset i.e. whether the disease began in the bulbar muscles or in the limbs. The study end-points were either death or tracheostomy. Therefore, the main outcome measure was tracheostomy-free survival. The median survival was 449 days and 532 days in the placebo and riluzole groups, respectively. Overall, riluzole therapy reduced mortality by 38.6% at 12 months and by 19.4% at 21 months (the end of the placebo-controlled period). However, the treatment effect was greater in patients with bulbar-onset disease than in patients with limb-onset disease.

The design of the second trial was similar to the first with the addition of a dose-ranging design and a longer period of evaluation.[16] In this study, randomization was stratified according to bulbar or limb onset of disease. The trial had a double blind, randomized and placebo-controlled four-arm design. The four groups compared treatments with placebo or 50mg, 100mg and 200mg riluzole daily. A total of 959 patients with clinically probable or definite ALS of less than 5 years duration entered the study. At the end of the study, defined by protocol as a median follow-up of 18 months, 122 placebo-treated patients (50%) and 134 of those who received 100mg of riluzole (57%) were alive without tracheostomy. In the groups receiving 50mg and 200mg riluzole daily, 131 (55%) and 141 (58%) patients were alive without tracheostomy. There was a significant inverse dose response in risk of death. No functional scale used in the study discriminated between the treatment groups. No beneficial effect on muscle strength, assessed by MRC scale, could be discerned in any treatment group.

Based on these results the ALS/Riluzole Study Group concluded that at a dose of 100mg per day, riluzole was an effective drug in slowing the progression of ALS to death, with an acceptable safety profile and represented the first step in the development of treatments for ALS. The effect was described as a reduction in the risk of death at 18 months of treatment, by about 35%. No difference was noted in the effect of treatment on the bulbar onset group as compared with the limb onset group.

Subsequent attempts to evaluate potential therapies for the amelioration of ALS have failed clinical trials. These molecules include anti-glutamate agents, despramipexole, minocycline, and idebenone. Edavarone has been found to be useful by some Japanese investigators but not replicated in trials in the Caucasian populations and its place in the therapy of ALS remains contentious.

## MADRAS MOTOR NEURON DISEASE

Meenakshisundaram, Jagganathan, and Ramamurthy designated the term "Madras Motor Neuron Disease" to a cohort of patients described by them in 1970. This term is applied to a sporadic, slowly progressive, juvenile onset of asymmetric weakness and wasting of the limbs accompanied by bilateral facial weakness, weakness and wasting of the tongue leading to bulbar dysfunction, and deafness in varying proportions.[17]

In contradistinction to ALS the clinical course of this disorder is benign and long-term survival over decades common.

Over a period of fifteen years, the original case series reported by Meenakshisundaram had been expanded to forty typical cases.[18] 70% of these forty patients exhibited clinical signs of lower cranial nerve dysfunction involving the 7th to 12th nerves in varying proportions. The presence of upper motor neuron signs may occur in up to 65% of cases thus making the resemblance to classical ALS very close. Therefore, in most discussions on MND/ALS, Madras Motor Neuron Disease (MMND) usually finds a place. The absence of reported identical cases from other parts of the world, the lack of established neuropathological correlates of the clinical features, and its rarity has shrouded a cloak of mystery over this elusive entity.

In the current understanding, Madras Motor Neuron Disease may be considered as a unique and variant form of anterior horn cell dysfunction with a phenotype that can be clinically recognized and distinguished from the standard motor neuron disease or ALS. Its prognosis and response to any therapeutic intervention are unknown.

## HIRAYAMA'S DISEASE/MONOMELIC AMYOTROPHY/ JUVENILE ASYMMETRIC SEGMENTAL MUSCULAR ATROPHY

In 1984, Gourie-Devi and her colleagues from NIMHANS, Bengaluru, described a sporadic condition that mimics motor neuron disease and designated the term "Monomelic amyotrophy" for this condition.[19] Japanese neurologists recognize this disorder as identical with that described by Keizo Hirayama in 1959[20] and in early medical literature it has been eponymously called Hirayama's Disease. The disorder reported by Singh et al, in 1980 is possibly the first Indian detailed study of this condition.[21] It is believed to be a disorder that occurs more commonly in the Asian sub-continent and Japan than in the Western world, though sporadic reports abound amongst the Caucasian population.

Patients with monomelic amyotrophy usually present to the neurologist in the second decade of life. The symptoms are characterised by a slowly progressive, asymmetrical weakness and wasting of the small muscles of the hands. The onset is usually unilateral and remains so for a long time. The wasting is typically restricted to the C7-T1 myotomes and only occasionally involves the C5-6 myotomes. Fasciculations occur and even when seemingly unilateral, electromyography may detect subclinical dysfunction in the opposite limb. Being insidious in onset, the wasting is clinically apparent by the time weakness is noticed by the patient. Often, there is a visible tremor in the outstretched affected limb or when an object is held in the affected limb. The deep tendon reflexes may be sluggish or absent in the symptomatic arm. Lower limbs, bulbar musculature, and the sensory system are unaffected.

The tempo of progression in this disorder is characterised by a plateau phase of clinical stabilization after the initial gradual worsening. There has been no documentation of weakness or wasting spreading to involve the lower limbs even decades after the affliction of the upper limbs. In the case series reported by Gourie-Devi et al, lower limb deep tendon reflexes were documented to be brisk in some patients.[19] This perhaps drew a close resemblance of this disorder to motor neuron disease. The authors also included three individuals with segmental lower limb weakness and wasting in their report. None of the other publications on this entity previously referred to as Hirayama's disease have reported lower limb dysfunction of this kind. The aetiology and pathogenesis of this condition remains an enigma.

Pradhan et al, from SGPGI, Lucknow performed magnetic resonance imaging (MRI) of the cervical spine in neutral and flexed positions in sixteen patients with Hirayama's disease, which they preferred to designate as juvenile asymmetric segmental spinal muscular atrophy (JASSMA). They took five normal individuals and five patients with ALS as their controls.[22] Focal atrophy of the lower cervical spinal cord was detected in patients with JASSMA. In flexion, there was a marked anterior displacement and antero-posterior flattening of the lower cervical cord against the vertebral bodies. The posterior dura mater also moved forward obliterating the subarachnoid space in all these patients. A large posterior epidural space was observed in flexion, which enhanced on administration of gadolinium in one of their patients. The authors suggested that these MRI characteristics are a hallmark of JASSMA, as such changes were not observed in either in their normal or ALS controls. Hirayama and Tokumaru reported a similar finding of marked forward displacement of the cervical dural sac and compressive flattening of the lower cervical cord

during flexion in seventy-three Japanese patients with Hirayama's disease.[23] Such features were not observed in twenty disease controls. The authors concluded that these radiological findings are supportive of the concept that this condition is a localized cervical poliomyelopathy, as postulated by them earlier.

Based on observations in two autopsied patients[24,25] who died from other causes, Hirayama proposed a phenomenon of chronic focal ischaemia of the cervical cord, perhaps as a result of repeated neck flexion in susceptible individuals as the aetiology of the unique neurological features of this disorder. However, other European workers were unable to replicate these MRI abnormalities in such patients[26, 27] raising doubts on the utility of performing cervical MRI as a surrogate test when this disorder is clinically suspected. The controversy may be related to the fact that a certain degree of symptomatic progression has to occur before radiological features are discernible.

Restuccia et al, studied somatosensory evoked responses in flexion and extension from the upper limbs in five patients with Hirayama's disease, six patients with ALS, and fourteen healthy individuals.[28] Neck flexion caused a significant amplitude decrease of the N13 cervical response only in patients with Hirayama's disease (and not in healthy controls or patients with ALS). They suggested that neck flexion resulted in electrophysiologically significant cervical cord dysfunction in patients with Hirayama's disease. This might be construed to reflect the effects traction on the cervical cord during flexion and its physiological effects on the vulnerable local segments in these patients.

In Hirayama's disease or JASSMA (as is the currently proposed nomenclature), there might be an option of surgically correcting the anatomical aberration of the flexion-extension abnormalities within the cervical cord, by decompressing the affected segments. This has been explored in various manners by speculative neurosurgeons with variable outcomes. While surgical decompression of the cervical cord has not become the standard of care,[29] the prospect of potential correction by such an intervention should be borne in mind when dealing with patients with this uncommon condition.

## JUVENILE ALS

Ben Hamida et al., described from Tunisia an unusual form of autosomal recessive, childhood onset motor neuron disease characterised by chronic slowly progressive degeneration of both upper and lower motor neurons.[30] The anatomical distribution of clinical features is identical to classical ALS. A combination of upper and lower motor neuron dysfunction often associated with pseudo-bulbar changes is characteristic of this form of 'juvenile ALS'. Cognitive and sensory functions are intact and survival over several decades is the rule. Genetic linkage of a large pedigree with juvenile ALS has defined a disease locus on the distal long arm of chromosome 2, mapping at 2q33-35.[31] Other Tunisian families with an identical clinical disorder[32] have been mapped to chromosome 15q12-21. Recently, a dominantly inherited eleven-generation

pedigree with juvenile ALS, having an English ancestry dating back to the 17th century, has been mapped[33] to chromosome 9q34. The phenotype of this family is similar to the phenotype of the Tunisian families though the modes of inheritance are different. In 1968, Shrivastava and Garg described a familial form of juvenile ALS[34] from North India that might be the only report of juvenile ALS similar to the ones described from Tunisia and USA.

The variability of clinical combination of features at a given time during the course of the illness, the broad spectrum of sporadic and inheritable disorders with such clinical features, and the occasional occurrence of symptomatic anterior horn cell disorders poses a challenge to most clinicians. A distinct understanding of these specific conditions aids correct nosologic designation and ultimate prognosis.

## REFERENCES

1. Aran FA Recherches sur une maladie non encore décrite du système musculaire (Atrophie musculaire progressive). *Arch Gen Med* 1850; 24:5-35,172-214.

2. Brain WR. Motor neuron diseases. In: Brain WR, editor. Diseases of the nervous system, 6th Ed. Ox ford: Oxford University Press,1962:531.

3. Rowland LP. Diverse forms of motor neuron disease. In: Rowland LP, editor. Human motor neuron diseases. New York: Raven Press:1982;1-13.

4. Mulder DW, Howard FM. Patient resistance and prognosis in amyotrophic lateral sclerosis. *Mayo Clin Proc* 1976; 51:537-541.

5. Neary D, Snowden JS, Mann DMA, et al. Frontal lobe dementia and motor neuron disease. *J Neurol Neurosurg Psychiatry* 1990; 53:23-32.

6. Abrahams S, Goldstein LH, Kew JJM, Brooks DJ, Lloyd CM, Firth CD, Leigh PN. Frontal lobe dysfunction in amyotrophic lateral sclerosis. A PET study. *Brain* 1996; 119:2105-2120.

7. Jackson M, Lennox G, Lowe J. Motor neuron disease-inclusion dementia. *Neurodegeneration* 1996; 5:339- 350.

8. Abrahams S, Goldstein LH, Al-Chalabi A, Pickering A, Morris RG, Passingham RE, Brooks DJ, Leigh PN. Relation between cognitive dysfunction and pseudobulbar palsy in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1997; 62:464-472.

9. Qureshi AI, Wilmot G, Dihenia B, Schneider JA, Krendel DA. Motor neuron disease with parkinsonism. *Arch Neurol* 1996; 53:987-991.

10. Desai J and Swash M. Extrapyramidal involvement in ALS: backward falls and retropulsion. *J Neurol Neurosurg Psychiatry* 1999; 67:214-216.

11. Younger DS, Chou S, Hays AP. Primary lateral sclerosis: a clinical diagnosis reemerges. *Arch Neurol* 1988; 45:13041307.

12. Pringle CE, Hudson AJ, Munoz DG, Kiernan JA, Brown WF, Ebers GC. Primary lateral sclerosis: clinical features, neuropathology and diagnostic criteria. *Brain* 1992; 115:495520.

13. Forsyth PA, Dalmau J, Graus F, Cwik V, Rosenblum MK, Posner JB. Motor neuron syndromes in cancer patients. *Ann Neurol* 1997;41:722730.

14. De Carvalho M, Dengler R, Eisen A, et al. Electrodiagnostic

criteria for the diagnosis of ALS. *Clin Neurophysiol* 2007; 119:497-503.

15. Bensimon G, Lacomblez L, Meininger V, ALS/Riluzole Study Group. A controlled trial of riluzole in amyotrophic lateral sclerosis. *N Engl J Med* 1994; 330:585-591.

16. Lacomblez L, Bensimon G, Leigh PN, ALS/Riluzole Study Group II. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. *Lancet* 1996; 347:1425-1431.

17. Meenakshisundaram E, Jaggannathan K, Ramamurthi B. Clinical pattern of motor neuron disease seen in younger age groups in Madras. *Neurol India* 1970; 18:109.

18. Jagannathan K and Kumaresan G. Madras pattern of motor neuron disease. In: Gourie-Devi M, editor. Motor Neurone Disease: Global Clinical Patterns and International Research. *New Delhi: Oxford & IBH* 1987:191-194.

19. Gourie-Devi M, Suresh TG, and Shankar SK. Monomelic amyotrophy. *Arch Neurol* 1984; 41:388-394.

20. Hirayama K, Toyokura Y, Tsubaki T. Juvenile muscular atrophy of unilateral upper extremity: a new clinical entity [in Japanese]. *Psychiatr Neurol Jpn* 1959; 61:2190-2198.

21. Singh N, Sachdev KK, Sushila AK. Juvenile muscular atrophy localized to the arms. *Arch Neurol* 1980; 37:297-299.

22. Pradhan S, Gupta RK. Magnetic resonance imaging in juvenile asymmetric segmental spinal muscular atrophy. *J Neurol Sci* 1997; 146:133-138.

23. Hirayama K, and Tokumaru Y. Cervical dural sac and spinal cord in juvenile muscular atrophy of distal upper extremity. *Neurology* 2000; 54:1922-1926.

24. Hirayama K, Tomonaga M, Kitano K, Yamada T, Kojima S, Arai K. Focal cervical poliopathy causing juvenile muscular atrophy of distal upper extremity: a pathological study. *J Neurol Neurosurg Psychiatry* 1987; 50:285-290.

25. Araki K, Ueda Y, Michinaka C, Takamasu M, Takino T, Konishi H. An autopsy case of juvenile muscular atrophy of unilateral upper extremity (Hirayama's disease) [in Japanese]. *J Jpn Soc Intern Med* 1989; 78:674-675.

26. Schroder R, Keller E, Flacke S, et al. MRI findings in Hirayama's disease: flexion-induced cervical myelopathy or intrinsic motor neuron disease? *J Neurol* 1999; 246:1069-1074.

27. Willeit J, Kiechl S, Kiechl-Kohlendorfer U, Golaszewski S, Peer S, Poewe W. Juvenile asymmetric segmental spinal muscular atrophy (Hirayama's disease): three cases without evidence of "flexion myelopathy". *Acta Neurol Scand* 2001; 104:320-322.

28. Restuccia D, Rubino M, Valeriani M, Mirabella M, Sabatelli M, Tonali P. Cervical cord dysfunction during neck flexion in Hirayama's disease. *Neurology* 2003; 60:1980-1983.

29. Agundez M, Ruoco I, Barcena J, Mateos B, Barredo J, Zarranz JJ. Hirayama disease: Is surgery an option? *Neurologia* 2015; 30:502-509.

30. Ben Hamida M, Hentati F, Ben Hamida C. Hereditary motor system diseases (chronic juvenile amyotrophic lateral sclerosis). *Brain* 1990; 113:347-363.

31. Hentati A, Bejaoui K, Pericak-Vance MA, Hentati F, Speer MC, Hung WY, Figlewicz DA, Haines J, Rimmler J, Ben Hamida C. Linkage of recessive familial amyotrophic lateral sclerosis to chromosome 2q33-35. *Nature Genetics* 1994; 7:425-428.

32. Hentati A, Ouahchi K, Pericak-Vance MA, Nijhawan D, Ahmad A, Yang Y, et al. Linkage of a commoner form of recessive amyotrophic lateral sclerosis to chromosome 15q15-q22 markers. *Neurogenetics* 1998; 2:55-60.

33. Rabin BA, Griffin JW, Crain BJ, Scavina M, Chance PF, and Cornblath DR. Autosomal dominant juvenile amyotrophic lateral sclerosis. *Brain* 1999; 122:1359-1550.

34. Garg B, Srivastava G. Familial juvenile amyotrophic lateral sclerosis. *Indian Pediatr* 1968; 5:119-121.