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Original Research Paper

Neurology

CLINICAL AND ELECTROPHYSIOLOGICAL PROFILE OF MOTOR NEURON DISEASE IN AN URBAN CENTER IN INDIA

Dr. Kapil Goel Senior Resident, Dept Of Internal Medicine, AFMC.

Dr. Y. S. Sirohi Prof Medicine And Neurology, Dept Of Internal Medicine, AFMC.

Dr. Rajagopal Srinath* Associate Prof Medicine And Neurology, Dept Of Internal Medicine, AFMC. *Corresponding author

ABSTRACT

BACKGROUND: Motor neuron disease (MND) is a relentlessly progressive neuro- degenerative disorder of either upper or lower motor neurons or both with worldwide incidence of approximately 1.2 per 1,00,000 and male/female ratio of approximately 1.8. Most cases are sporadic (90-95%) whereas 5-10% are familial, [1,2] usually with autosomal dominant transmission. An unusual form of MND occurs in the Western Pacific associated with parkinsonism and dementia.[3] Most cases do not progress to typical MND.[4] Despite the disabling nature of MND, there is limited data available from one of the largest state of India. Thus, the present study aimed at reporting clinical characteristics and electrophysiological profile of MND patients and also to determine pattern of MND from Maharashtra, India. **MATERIAL AND METHODS:** This study has been conducted in Department of Internal Medicine at tertiary care centre in 2018-2019 at Maharashtra. A total of 30 patients of MND were enrolled in the present study. The clinical characteristics including occupational history and various risk factors with detailed neurological examination were systematically recorded. Nerve Conduction Studies and electromyography has been conducted on EB Neuro machine placed in department of neurology at the study centre. **RESULTS:** Amyotrophic Lateral Sclerosis (ALS) and Monomelic Amyotrophy (MMA) variety are the two most common variants, 27 out of 30, in our study. Out of these, 17 patients belong to MMA variant and 10 patients detected to have ALS. 11 patients out of 17 patients of MMA had upper limb involvement. Male to female ratio was 9: 1. Mean age of MND patients was 39 ± 12 (17-66 years). Age of onset of symptoms in majority lies between 15-40 yrs in MMA group while > 30 yrs in ALS type, suggesting earlier age of onset of symptoms in MMA variety. Limb onset was seen in 28 (93%) and bulbar onset in 2 (7%) of patients. No familial association was found. Trauma was the commonest environmental factor found in MND patients which was reported by 10 patients in our study. In 5 patients, nerve conduction velocity found to be decreased; however, it was not much significant as to exclude the diagnosis of ALS. In motor nerve conduction studies, 10 patients showed axonal neuropathy changes with decreased amplitude and increase distal latency and 7 out of these 10 patients belonged to ALS variant. 1 patient has demyelinating changes. It is also observed that the changes are more prominent in clinically more weaker muscle as per MRC grading. Electromyography show neurogenic pattern in patients. Fibrillation and positive sharp waves suggesting active denervation present in 15 out of 17 patients of MMA variant in affected limbs.

KEYWORDS : Motor Neuron Disease, Amyotrophic Lateral Sclerosis, Electromyography

INTRODUCTION

MNDs mostly are diffuse system degenerations of unknown etiology that selectively destroy upper and/or lower motor neurons.[5,6] Many of MNDs are diffuse, sporadic, and progressive, however, some of them is hereditary[7,8] or focal.[9] Amyotrophic lateral sclerosis(ALS) is the most common MND in adults and spinal muscular atrophy (SMA) is the most common in children.[10,11]In one form of hereditary ALS, underlying molecular genetic defect with an abnormal form of the enzyme superoxide dismutase has been identified.[12]

Anterior horn cells (AHCs) can be damaged in neoplasms, after radiation, asthma, and hypoglycaemia. [13,14,15,16]

MNDs generally do not show clinical involvement of the sensory or other components of the nervous system. Some forms of MND selectively affect the upper motor neurons as in primary lateral sclerosis; some selectively affect the lower motor neurons, as in progressive SMA; others, such as Kennedy's syndrome, have specific distribution and in the most common disorder, ALS, there is involvement of both upper and lower motor neurons. Involvement of upper motor neurons results in weakness without atrophy, brisk reflexes and presence of pathologic reflexes. Spasticity is common and patient can have spastic dysarthria with pseudobulbar palsy, or spastic gait, which suggests involvement at multiple levels. On needle electromyography (EMG), abnormalities of motor unit discharge patterns suggest upper motor neuron involvement. In lower motor neuron damage in ALS, degeneration of AHCs and their peripheral axons results in loss of muscle innervations as a result of which denervated muscle becomes weak, flaccid, and atrophic. The nerve terminals of remaining intact motor units retain their capacity for collateral sprouting and will reinnervate the denervated muscle fibres. Approximately, half of the motor neurons innervating a muscle must be lost in ALS before clinical signs of weakness or atrophy are found.[17] The regenerating axons are irritable and often discharge spontaneously which results in fasciculations.

Progressive muscular atrophy consists of lower motor neuron involvement of limb muscles, without definite evidence of upper motor neuron features, however, the tendon reflexes are brisk even in the wasted muscles, which differentiate it from progressive spinal muscular atrophy, in which the tendon reflexes are usually reduced. It commences after age of 20 years and has no familial association.[18]

Primary lateral sclerosis consists of a slowly progressive spastic paraparesis with only corticospinal tract involvement and no other signs on examination. It generally begins in adult life. Familial spastic paraplegia is excluded by absence of a family history of the disorder, and investigation reveals no other abnormality. EMG evaluation reveals no evidence of lower motor neuron disturbance. Other differentials like Multiple sclerosis, HTLV-I associated tropical spastic paraparesis and AIDS myelopathy must be excluded by MRI and serological tests before considering this diagnosis. Some patients may have associated pseudo bulbar palsy. There are usually mild corticospinal abnormalities in the upper limbs. The disorder progresses slowly for up to 20 years in some studies.[19]

Hirayama Disease is predominantly distal form of MND, of

juvenile onset, usually confined to one upper limb.[20]It is more common in Japan,[20,21] Srilanka[22]and India. More common in males especially for cases involving the upper limb.Onset is before the age of 30 years. This disorder usually confined to one upper limb for a period of about 2 years before progression occurs with involvement of proximal forearm muscles, and of the opposite arm. Tremor develops in the affected limbs and the tendon reflexes are reduced. In 15% of cases, the disease arrests within 5 years of its onset.

Madras form of MND is a sporadic disorder of young adults, with generalised neurogenic atrophy, bulbar palsy and sensorineural deafness, but with a benign course.[23,24]There is sparing of cognitive function, sensory system and other parts of neuraxis.

Monomelic amyotrophy (MMA) involves wasting and weakness which usually restricts to a single upper or lower limb. It is more common in young male. There is evidence of LMN involvement, and it has very slow course. Bulbar cranial nerves, cerebellar, extra pyramidal, pyramidal and sensory system are spared.

Outcome of MND- The duration of the disease from diagnosis is approx. 1 to 5 years, with a median survival of about 2 years.[25] Patients with amyotrophic lateral sclerosis had a mean survival of 3.3 years, and those with bulbar symptoms survived 2.2 years.[26]Earlier the age of onset the longer the survival, and atypical juvenile-onset, monomelic MND has a benign course. Progressive muscular atrophy and primary lateral sclerosis have a relatively benign outcome with survival for 10 years or more.

MATERIAL AND METHODS

Study Design

This study has been conducted in a single center tertiary care at Maharashtra. This study was carried out from Dec 2017 to Dec 2019 in the Armed Forces Medical College, Pune (Maharashtra). In the present study, we describe the clinical and electrophysiological profile of motor neuron disease patients.

Ethical Clearance

The clearance from Institutional Ethics Committee was obtained prior to the conduct of study.

Study Population

Patients presenting to neurology department at tertiary care centre who fulfilled revised El Escorial criteria for Amyotrophic Lateral Sclerosis, Pringle criteria for Primary Lateral Sclerosis and with clinical suspicion of other variants of motor neuron disease have been enrolled for the study. Informed consent has been taken from all patients included in the study. There was no control group in the study. Patients having compressive myelopathy, Hyperthyroid patients, Diabetic patients and Lymphoma patients have been excluded from the study.

Study Tools

The study tools that were used were the instruments required for routine neurological examinations. Nerve Conduction Studies and electromyography has been conducted on EB Neuro machine placed in department of neurology at the study centre.

Data Collection

A pre-designed proforma as attached in annexure A was used to record relevant information from the individual patients selected. Name, age, sex was noted. A detailed history of presenting complaint and any history pertaining to neurological deficit was considered. A detailed general, systemic and neurological examination has been carried out in all the selected patients.

Investigations

Routine haematological and biochemical parameters and other investigations like ESR, TSH, Blood sugar F/PP, Chest X ray- PA view, X-ray cervical and lumbar spine antero-posterior and lateral view as per proforma attached in Appendix B was done at standard laboratory to rule out other conditions that mimic the findings of motor neuron disease.

Sensory nerve conduction studies carried out for bilateral ulnar nerve, median nerve and sural nerve by placing electrodes over 5th finger, 3rd finger and lateral malleolus. Motor nerve conduction studies carried out for median nerve at abductor pollicis brevis at wrist and above elbow, for ulnar nerve at adductor digiti minimi at wrist and below ulnar groove, for tibial nerve in abductor hallucis at medial malleolus and popliteal fossa and for peroneal nerve in extensor digitorum brevis at ankle and below fibular head.

Electromyography carried out for all 4 regions- bulbar region, cervical region, thoracic region and lumbar region. Genioglossus muscle, deltoid muscle, abductor pollicis brevis, paraspinal muscle at T10, vastus lateralis and tibialis anterior was evaluated of the affected side. All studies have been carried out with the same equipment in same settings to avoid technical factors influencing the study. For the paraspinal thoracic muscles, the patient was asked to lie prone, with a soft cushion under the abdomen and to relax the head, shoulders and arms towards the floor. If patient was not comfortable in this position, the patient asked to lie on one side with the spine bent. Denervation was defined as the occurrence of spontaneous muscle fiber activity like fibrillations, positive sharp waves, or complex repetitive discharges in at least one of the insertion site. Reinnervation was defined as the occurrence of an abnormally long mean motor unit potential duration, or an abnormally large proportion of MUPs that were polyphasic or an abnormally large proportion of giant MUPs which was defined as amplitude exceeding 7mV. Polyphasia is defined by greater than four phases in a MUP and may occur normally up to 10% of the MUPs in any given muscle, and up to 25% in the deltoid. At least 10-20 MUPs were sampled during slight voluntary contraction for each muscle tested and only MUPs with high frequency content were taken into account. The mean MUP duration and the proportion of polyphasic or giant MUPs were estimated on visual inspection. If enough MUPs could not be sampled during slight voluntary contraction, additional MUPs by voluntary contraction at higher force levels was attempted including maximal voluntary contraction if necessary. In case of requiring maximal voluntary contraction, half of the MUPs had to be polyphasic or of giant amplitude and these MUPs had to occur in a single or poorly mixed pattern to fulfil the criteria for reinnervation.

Statistical Analysis

The descriptive statistics of the study population were reported as counts and percentages for categorical variables and mean ± standard deviation for continuous variables with normal distribution.

RESULTS

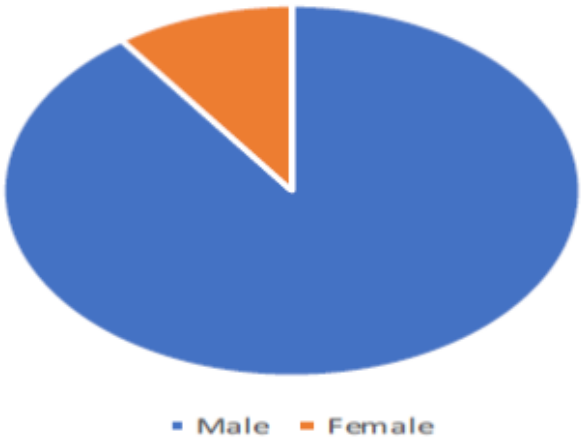
Demographic Presentation

Male is to female ratio is 9:1. Male are more affected than females (Figure 1). Mean age of MND patients was 39 ± 12 (17-66 years). Age of onset of symptoms in majority lies between 15-40 yrs in MMA group while > 30 yrs in ALS variants, suggesting earlier age of onset of symptoms in MMA variety (Table 1). No familial association was found. In our study, most of the patients were drivers (10 in our study). In the students (4 in our study), MMA variant was the most common (3 out of 4). Occupation of the other patients were as 1 chef, 2 clerk, 1 construction worker, 1 electrician, 3 army, 4 farmers, 2 housewife and 2 gatekeepers.

Onset
Limb onset was seen in 28 (93%) and bulbar onset in 2 (7%) of patients (Table 2).

Risk Factors
Trauma was the commonest environmental factor found in MND patients which was reported by 10 patients in our study (Table 3).

Presenting Complaint
Weakness and wasting in limbs was chief complaint 23 of patients followed by both weakness in limbs and slurring of speech in 5 patients and slurring of speech and difficulty in swallowing 2 patients, respectively.



(Figure 1)

Table 1: Age and gender distribution of MND patients

Age at Onset (yrs)	ALS		PMA		PLS		MMA	
	Male	Female	Male	Female	Male	Female	Male	Female
15-30	3	0	1	0	0	0	5	1
31-40	1	2	0	0	0	0	7	0
41-50	1	0	0	0	0	0	1	0
51-60	2	0	1	0	1	0	3	0
>60	1	0	0	0	0	0	0	0

Table 2 : Involvement at disease onset

Involvement at Onset	ALS	PMA	PLS	MMA
Limbs	3	2	1	17
Bulbar	2	0	0	0
Limbs + Bulbar	5	0	0	0

Table 3 : Risk Factors

Risk Factor	ALS	PMA	PLS	MMA
Mechanical Injury	3	0	0	7
Surgery	2	0	0	1
Poliomyelitis	0	0	0	0
Tobacco Chewing	1	0	1	1
Alcohol Drinking	1	0	0	0

Duration of Symptoms before presentation
The time interval from the onset of symptoms to first presentation to the hospital for different types of motor neuron disease is shown in Table 4. Mean duration of symptoms were 18.7 months with range from 1-100 months. It is observed that 6 out of 10 patients reported within 12 months from the onset of symptoms in ALS variant, however, in MMA variant, patient reported from onset of symptoms tends to be delayed, only 5 out of 17 patients reported within 12 months and majority that is 10 out of 17 patients reported between 12-24 months duration of symptoms. This may be due to slow progression seen in MMA variety.

Clinical Examination
Maximum number of patients had wasting of the upper limb on clinical examination followed by lower limb. Also tongue fasciculations was found in 50% of patients on examination. Polyminimyoclonus have been noted in 2 patients with Hirayama variant of MMA. Power was found to be relatively preserved even in severely wasted limb. No sensory abnormality was noted in any of the patient.

Investigations
Hematological and biochemical parameters of the patients were within normal limits.

Sensory nerve conduction studies found to be normal in all nerves tested in all variants of MND except in 5 patients in whom nerve conduction velocity found to be decreased; however, it was not much significant as to exclude the diagnosis of ALS. Distal latency and sensory nerve action potential amplitudes are within normal range in all nerves in all variants of MND.

In motor nerve conduction studies, 10 patients out of 30 showed axonal neuropathy changes with decreased amplitude and increase distal latency and 7 out of these 10 patients belonged to ALS variant. 1 patient has demyelinating changes. It is also observed that the changes are more prominent in clinically more weaker muscle as per MRC grading.

Electromyography show neurogenic pattern in patients. Genioglossus muscles tested in case of ALS patients showed fasciculations in all patients of this variant.

In the monomyelic amyotrophy group, EMG and NCV were done in both affected as well as unaffected limbs. Fibrillation and positive sharp waves suggesting active denervation present in 15 out of 17 patients of MMA variant in affected limbs, however, no evidence found on unaffected side. In a small portion of clinically affected limb regions, no denervation or reinnervation was found and it may be caused by the investigation of few instead of all muscles in an affected region. In addition, denervation or reinnervation may not be found in grossly atrophic muscles.

DISCUSSION
Incidence of MND in India ranges from 0.06% to 0.11% of all neurological cases presented to outpatient department as recorded in various studies in different parts of the country like Chopra et al.[27] at north India, Bharucha et al.[28] at west India, Wadia et al.[29] at central India, Saha et al.[30] at east India and Gourie Devi et al.[31] at south India. Prevalence of MND ranges from2.86 per 100,000 in rural Bengal study conducted by Das et al. [32] to 4 per 100,000 in Bangalore study conducted by Gourie Devi et al. [31] The incidence in various studies varied due to different sources of data collection.

In this study, monomelic variety constitutes majority of cases followed by ALS. The present study showed male predominance with male: female ratio of 9:1. On review of literature, various studies in western literature reports male predominance ranging from 1.2: 1 to 20: 1 although some studies show no sex difference or even a female predominance.

The age of onset is <60 years for patients with ALS with most of the patients in 41-50 age group. This is in consistence with other studies conducted in India and it is noted that the mean age of onset of MND in India tends to be one decade earlier than that in most western countries. This may be attributed to a larger younger population of our country.

In our study, there was no positive family history in any of the patients. In one study conducted by Leigh and Roy

Chaudhuri,[33] autosomal dominant inheritance reported in 5-10% of patients suffering from ALS, however, familial clustering in this study was not found as in previous studies from India.

In our study, both sedentary workers and hard physical labourers are equally affected in all the variants of MND. History of mechanical injury was present in 3 of ALS patients and 7 monomelic amyotrophy patients. Similar findings noted by Gourie Devi[31] and Saha et al.[30] from India and Kondo and Tsubaki[34] from Japan. However, there was no correlation with site of trauma with initial manifestation of MND.

Weakness and wasting were found in more than 80% of patients and it is comparable with other studies of India like Chopra et al. [27], Bharucha et al. [28], Wadia et al. at [29], Saha et al. [30] and Gourie Devi et al. [31]

Fasciculation wasfound in 57% patients with ALS and these results are comparable to Saha et al. (52.8%),[30] however, less than that found by Chopra et al. (80.48%).[27] Polyminimyoclonus have been noted in 2 patients with Hirayama variant.

Bulbar symptoms were present only in ALS patients in 70% of patient which is comparable to other studies like Gourie Devi [31] and Saha et al. [30]

No sensory signs and symptoms were present in any of the patients in all the variants. Although some of the patients complain of vague muscle aches.

Progression of wasting and weakness was very slow in MMA cases. These are the patients who presented with wasting and weakness restricted to either a single upper or a lower limb. There is male predominance. These constitute 60% of the cases reported in our study. Gourie Devi coined the term "Monomelic Amyotrophy" for such type of cases. Hirayama disease as reported by Hirayama et al. from Japan and wasted leg syndrome as reported by Prabhakar et al. have been included as monomelic amyotrophy variant of motor neuron disease in our study. According to study done by Chopra et al., it is noted that heavy manual exertion may be responsible for initiation of the disease process of wasted leg syndrome. In our study, most of the patients of MMA are involved in some form of heavy work. There is no involvement of other limb either clinically or electromyographically in these patients. Wasting and weakness was predominantly distal and intrinsic small muscles of hand and foot are particularly the most affected. There might be some environmental factors which are responsible for a greater number of cases of monomelic amyotrophy in this part of the country as compared to others.

No patient with features suggestive of Madras pattern of MND was noted in the study period. Most of the cases of Madras MND have been reported from Tamil Nadu although there are few reports from other parts of India.

EMG pattern was neurogenic in most patients in all variants of MND. Motor and sensory conduction velocity was essentially normal in all the MND patients. Active denervation with fibrillation and positive sharp waves were seen in most of the patients of monomelic amyotrophy. Chronic denervation was found in all patients.

CONCLUSION

This study has been conducted at tertiary care centre in Maharashtra state. There are more patients of monomelic amyotrophy as compared to other variants as noted in the study. There is male predominance and male:female ratio of 9:1 observed in this study. Age of onset is in 5th decade for ALS group and 3rd to 4th decade that is 1-2 decades earlier than ALS group for MMA variant. Weakness and significant wasting are the predominant symptoms reported by the patients. History of mechanical trauma found to be more in MMA group than other group, however, site of injury is not correlated with the disease process. No familial association noted in any of the variants.

Neurogenic pattern that is active with chronic denervating changes is seen on needle electromyography in these patients. No evidence of neurogenic changes seen on unaffected limbs in case of MMA variety. Some patients shows axonal neuropathic changes on nerve conduction studies.

LIMITATIONS

The small sample size and study participants from one center are the main limiting factors in our study.

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