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Clinical Profile of Various Mnd Cases That Presented to A Tertiary Centre Over the Past 3 Years

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Abstract

INTRODUCTION:

Motor neurone disease (MND) is a disabling and ultimately fatal disease of the motor system, with few effective treatments. Considerable heterogeneity is observed in the clinical motor features of MND, with extra-motor manifestations now also recognized as part of the condition. Progressive motor weakness and bulbar dysfunction lead to premature death, usually from respiratory failure. Diagnosis remains clinical. There are no specific laboratory markers which make the diagnosis independent of the clinical pattern but there are a few appropriate investigations to exclude mimics. The clinical syndrome once observed is recognized easily because of a distinctive appearance and course.

OBJECTIVES:

To demonstrate and compare the etiology, demography & clinical profile of various forms of Motor Neuron Diseases

DESIGN:

Cross sectional (Observational) study

SETTING:

Sapthagiri Institute of Medical Sciences & Research Centre

METHODS:

30 MND cases diagnosed clinically (as per Awaji-Shima modification of the El Escorial Criteria) with few supportive investigations that presented to our centre over the past 3 years were compiled and compared

CONCLUSIONS:
Mortality rates in MND depends on type of MND and subtypes like Madras Motor Neuron disease, SMA, PLS has the slowest progression and best prognosis of all the subtypes. Secondary MND due to exposure to heavy metals has faster progression and worst prognosis

Keywords: Motor neuron disease, Amyotrophic lateral sclerosis, Spinal muscular atrophy

INTRODUCTION:

- Motor neuron disease (MND) is an adult-onset neurodegenerative disorder characterized by loss of upper motor neurons (UMNs, including the Betz cells of the motor cortex), and lower motor neuron (LMNs, anterior horn cells of the spinal cord and brainstem nuclei) with an average survival being between 2 and 3 years[1]
- The adult-onset, idiopathic motor neuron diseases (MND) comprise: Predominantly LMN : Progressive Muscular Atrophy, Spinal Muscular Atrophy & Progressive Bulbar Palsy; Predominantly UMN: Primary Lateral Sclerosis & Pseudobulbar Palsy; the generalized disorder with all these characteristics, amyotrophic lateral sclerosis (ALS)[2].
- ALS is considered to occur throughout the world, especially in Africa, India and China, where systematic epidemiology has not yet been carried out[1]
- The mean age of onset of MND is a decade earlier in India than that in most other countries. Predominant affection of younger patients may be due to a larger younger population of our country[3]
- Most cases are sporadic (90–95%) whereas 5–10% are familial usually with autosomal dominant inheritance. Death from respiratory failure usually follows within 5 years of onset[4]
- Motor Neuron Disease (MND) patients are accorded different levels of diagnostic certainty (definite, probable, possible and suspected) as per El Escorial criteria (EEC)[4]
- Extra-motor cerebral pathology, even if not always clinically obvious, is routinely observed on histopathology. This is associated with variable dysexecutive impairment and behavioral disturbance, and in up to 15% there is overt frontotemporal dementia (FTD), with a predilection for the prefrontal, frontal and temporal cortices[1]

ALS:

- The term ALS includes the complete spectrum with typical upper and lower motor neuron involvement, progressive muscular atrophy, bulbar and pseudobulbar palsy[4]
- Most patients demonstrate combined LMN-related loss of muscle as a result of denervation (amyotrophy), and UMN degeneration of the lateral corticospinal tract and its cortical origins manifesting as gliosis, or hardening (sclerosis)[1]
- Classical ALS has approximately an annual incidence of 1/100,000 population, a prevalence of 4/100,000, a male to female ratio of 1.5 to 2:1, a mean age of onset of 56 years, a mean duration of illness of 2.5 years and a mean age at death of 59 years[4]
- Younger age of onset is widely recognized to be associated with longer survival[4]
- Exercise intolerance and fatigue, volitional cramps are common early symptoms of ALS. The classical findings include spasticity and brisk reflexes (features of UMN involvement) along with wasting, asymmetric weakness and/or fasciculations (features of LMN involvement) in the same body segment.

- Wasting of the intrinsic small muscles of the hand is common; particularly flattening of the thenar eminence and the first dorsal interosseous muscle. In the lower limbs early symptoms include foot drop, a sensation of heaviness of one or both legs, or a tendency to trip. Patients may also notice difficulty in rising from low chairs and climbing stairs or excessive fatigue when walking. On examination muscle wasting is often seen in the tibialis anterior[5]
- Bulbar onset motor neuron disease occurs in about 20% of those affected. The first sign is usually slurring of the speech, caused by impaired tongue movement, which may be accompanied by obvious wasting and fasciculation of the tongue. Dysphagia tends to occur later, when speech difficulties have become significant. Bulbar symptoms in motor neuron disease, as with other causes of pseudobulbar palsy, are often associated with emotional lability, manifesting as inappropriate laughing or crying[5].
- The least common pattern of onset is when the respiratory muscles are affected first[5].

MADRAS MOTOR NEURON DISEASE:

- In 1970, the first description of Madras motor neuron disease (MMND) was given by Meenakshisundaram et al., from Madras (now called Chennai) located in Southern India[6].
- The disease manifests in young individuals with clinical features of a thin habitus, wasting and weakness predominantly of distal muscles of limbs, involvement of facial and bulbar muscles, pyramidal dysfunction and can be associated with optic atrophy (MMND variant) and sensorineural hearing impairment[6].
- The disease was described as a sporadic disorder with benign course[6]
- Survival is long, and in a 36yrs long study done in NIMHANS, it was observed that among the expired group the minimum survival was 12 months and maximum of 371 months. For men it was 96 and 324 months, for women 12 and 371 months. Among the living patients the maximum survival was 459 months, which was seen among men, and for women it was 312[6]

MATERIALS AND METHODS:

- This is a Cross sectional study where we have reviewed the clinical data on 30 patients of MND, presenting to our tertiary care institute of South India (Sapthagiri Institute of Medical Sciences and Research Centre, Bengaluru) over a period of 3 years.
- Onset, progression, social, demographic, clinical profile, prognosis, etiology was compiled, studied and compared across all the cases
- All patients initially underwent a detailed history taking and examination, later patients underwent routine blood investigations (including Lead and Aluminum levels), chest X-ray, neuroimaging.
- NCS and EMG studies were performed on each patient according to established techniques. At least three body regions were assessed in every patient – bulbar, cervical, thoracic, paraspinal, and lumbosacral. Spontaneous activity in the form of fibrillations, PSWs during EMG was considered consistent with denervation.
- Periodic follow up via OPD visits and telephonic calls were performed for patients who are still alive.

- **INCLUSION CRITERIA:**
- All patients with clinically definite and probable MND presenting to the institute were included in the study, diagnosed according to as per the Awaji-Shima modification of the El Escorial Criteria[7]

- **EXCLUSION CRITERIA:**
- Patients with clinically possible ALS were excluded.
- Patients with established neurological diagnosis other than MND were excluded
- All eligible patients/ attendees had to sign an informed consent form

SUMMARY OF THE CASES

CASES	AGE OF ONSET	GENDER	PRIMARY OR SECONDARY TO	VARIANT	DURATION OF	TYPE OF OCCUPATION	PREDOMINANT	LIMB ONLY/ LIMB + BULBAR	KING'S STAGING	ALIVE OR DEAD	CAUSE OF DEATH
1	56	M	SECONDARY TO	ALS	6M	PHYSICAL (PAINTER)	WEAKNESS	LIMB + BULBAR	5	DEAD	ASPIRATION
2	61	M	PRIMARY	ALS	11M	PHYSICAL (FARMER)	WEAKNESS	LIMB + BULBAR	5	DEAD	RESPIRATORY FAILURE
3	35	M	PRIMARY	MMNDV	10Y	PHYSICAL (FARMER)	WASTING	LIMB ONLY	2	ALIVE	-
4	45	M	SECONDARY TO	ALS	8M	PHYSICAL (PAINT SHOP OWNER)	WASTING	LIMB + BULBAR	5	DEAD	RESPIRATORY FAILURE
5	50	M	PRIMARY	ALS	4M	PHYSICAL (CARPENTER)	WEAKNESS	LIMB + BULBAR	5	DEAD	ASPIRATION
6	18	F	PRIMARY	SMA	20Y	SEDENTARY (STUDENT)	WASTING	LIMB ONLY	2	ALIVE	-
7	50	M	PRIMARY	MMND	6Y	PHYSICAL (FARMER)	WASTING	LIMB ONLY	2	ALIVE	-

8	46	M	SECONDARY TO LEAD	ALS	3M	PHYSICAL (PAINTER)	WEAKNESS	LIMB + PSEUDOBULBAR	5	DEAD	RESPIRATORY FAILURE
9	53	M	PRIMARY	ALS	1Y	PHYSICAL (LABOURER)	WEAKNESS	LIMB + BULBAR	5	DEAD	ASPIRATION
10	62	M	SECONDARY TO	ALS	8M	PHYSICAL (FARMER)	WASTING	LIMB ONLY	3	ALIVE	-
11	68	M	PRIMARY	ALS	3Y	PHYSICAL (ESTATE MANAGER)	WASTING	LIMB + BULBAR	2	DEAD	ASPIRATION
12	56	F	PRIMARY	ALS	4Y	PHYSICAL (HOUSE WIFE)	WASTING	LIMB + PSEUDOBULBAR	5	DEAD	RESPIRATORY FAILURE
13	44	M	SECONDARY TO	ALS	6M	PHYSICAL (PAINTER)	WASTING	LIMB + PSEUDOBULBAR	5	DEAD	RESPIRATORY FAILURE
14	59	M	PRIMARY	PLS	6Y	PHYSICAL (FARMER)	WEAKNESS	LIMB ONLY	2	ALIVE	-
15	52	M	PRIMARY	ALS	4Y	PHYSICAL (LABOURER)	WASTING	LIMB + BULBAR	5	DEAD	ASPIRATION
16	62	M	PRIMARY	ALS	3Y	PHYSICAL (CIVIL ENGINEER)	WASTING	LIMB + BULBAR	5	DEAD	ASPIRATION

17	55	M	PRIMARY	ALS	10Y	SEDENTARY (DOCTOR)	WASTING	LIMB + BULBAR	5	DEAD	ASPIRATION
18	58	M	PRIMARY	ALS	2Y	PHYSICAL (LABOURER)	WASTING	LIMB + BULBAR	5	DEAD	DCLD (OTHER CAUSE)
19	53	M	PRIMARY	ALS	4Y	PHYSICAL (LABOURER)	WASTING	LIMB + BULBAR	5	DEAD	ASPIRATION
20	58	F	PRIMARY	ALS	3Y	PHYSICAL (GARMENTS WORKER)	WEAKNESS	LIMB + PSEUDOBULBAR	5	DEAD	RESPIRATORY FAILURE
21	46	M	PRIMARY	ALS	4Y	PHYSICAL (PLUMBER)	WEAKNESS	LIMB + BULBAR	5	DEAD	ASPIRATION
22	48	M	PRIMARY	ALS	3Y	PHYSICAL (LABOURER)	WASTING	LIMB + BULBAR	5	DEAD	RESPIRATORY FAILURE
23	60	F	PRIMARY	ALS	2Y	PHYSICAL (HOUSE WIFE)	WEAKNESS	LIMB + BULBAR	5	DEAD	ASPIRATION
24	54	M	PRIMARY	ALS	5Y	PHYSICAL (FARMER)	WASTING	LIMB + BULBAR	5	DEAD	ASPIRATION
25	59	M	PRIMARY	ALS	1Y	SEDENTARY (BANK CLERK)	WASTING	LIMB + PSEUDOBULBAR	5	DEAD	RESPIRATORY FAILURE
26	42	M	SECONDARY TO LEAD	ALS	5M	PHYSICAL (PAINTS / SOLVENTS FACTORY WORKER)	WEAKNESS	LIMB + BULBAR	5	DEAD	ASPIRATION

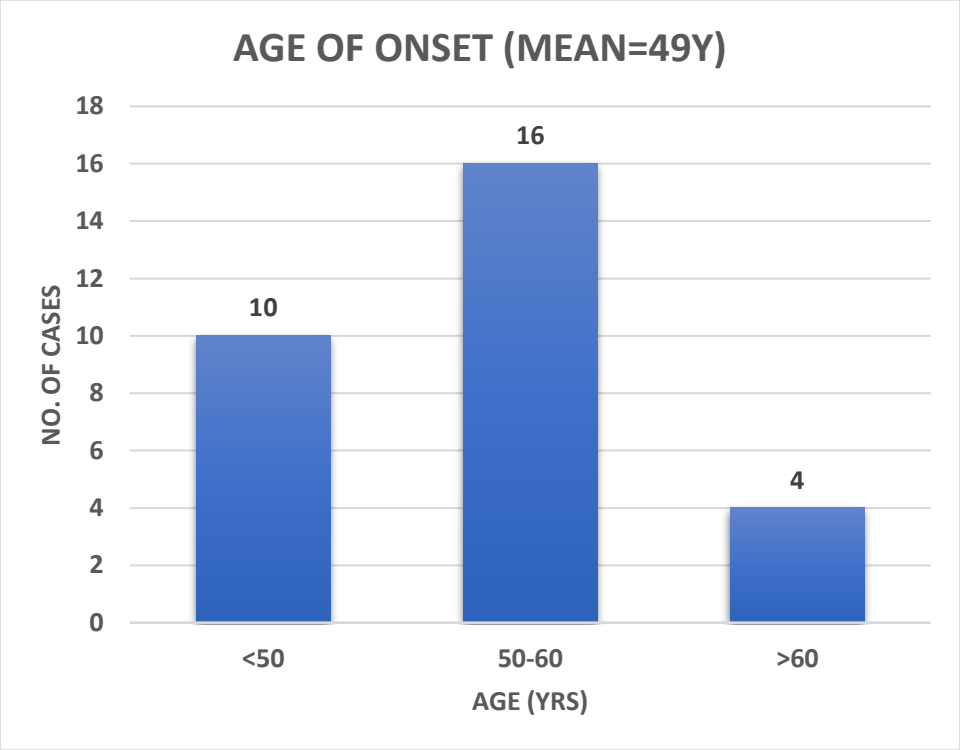
27	49	M	PRIMARY	ALS	4Y	PHYSICAL (FARMER)	WEAKNESS	LIMB + BULBAR	5	DEAD	ASPIRATION
28	48	M	PRIMARY	ALS	3Y	PHYSICAL (FARMER)	WASTING	LIMB + BULBAR	5	DEAD	ASPIRATION
29	55	M	PRIMARY	MMND	8Y	PHYSICAL (LABOURER)	WASTING	LIMB ONLY	2	ALIVE	-
30	52	M	PRIMARY	ALS	3Y	PHYSICAL (FARMER)	WASTING	LIMB + PSEUDOBULBAR	5	DEAD	RESPIRATORY FAILURE

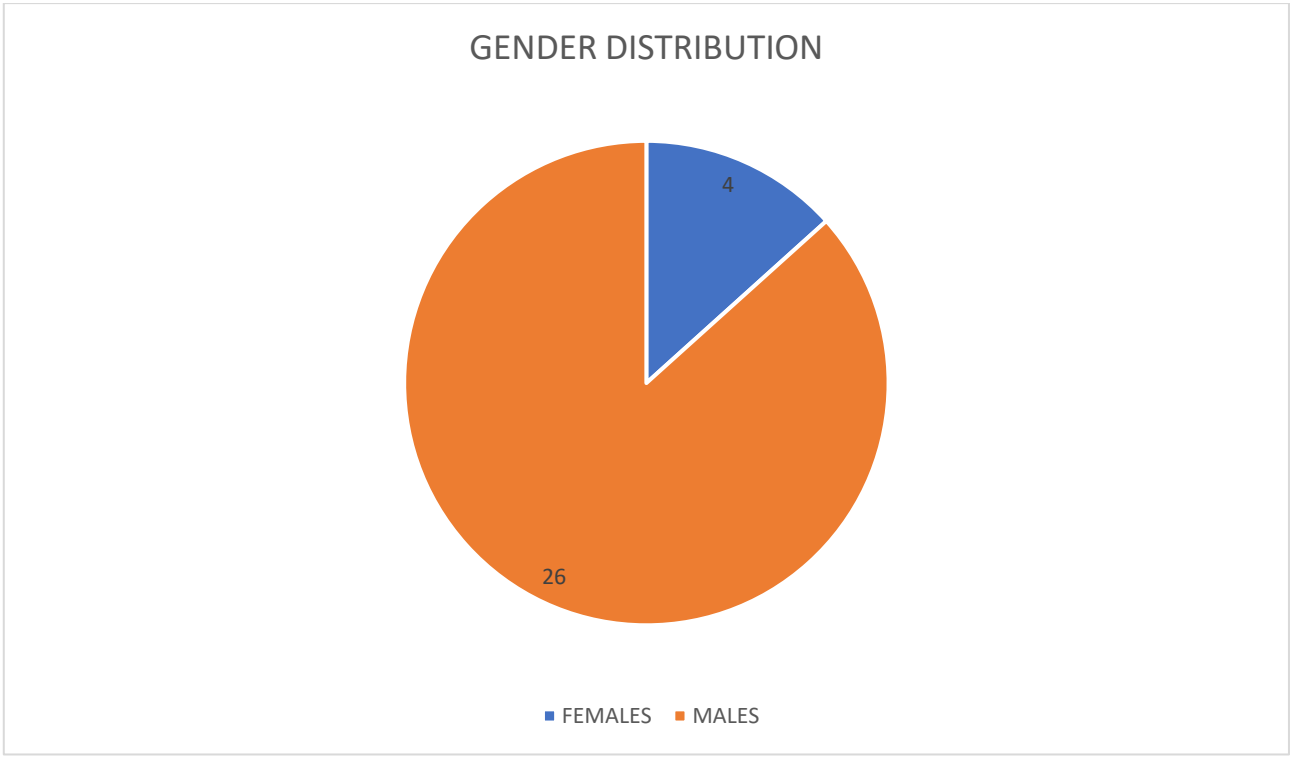
RESULTS:

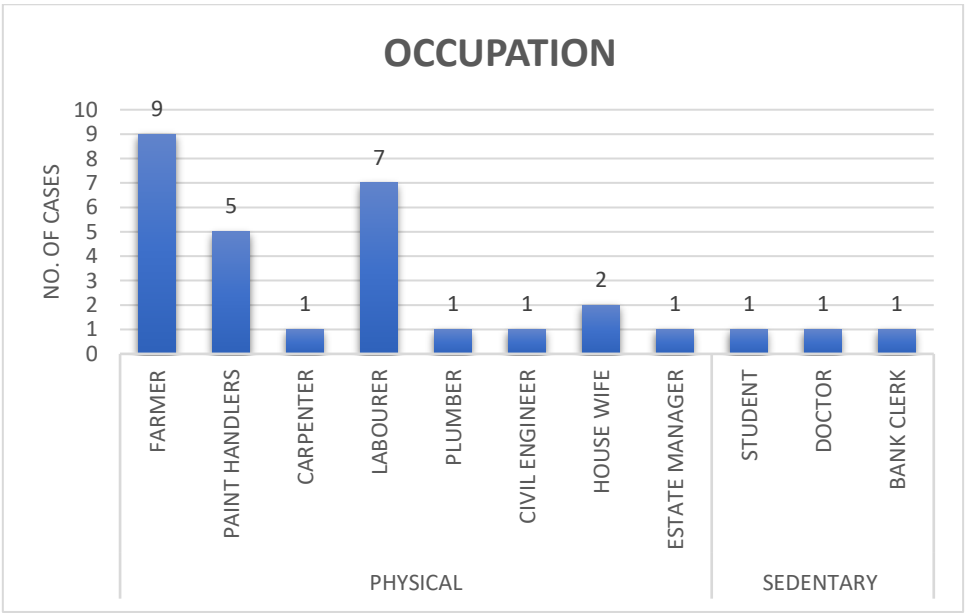
- Mean age of onset was found to be 51.8 yrs with lowest of 18y and highest of 68 yrs. 16 out of 30 cases were aged between 50 to 60 yrs at onset
- 26 cases were males and 4 were females
- 24 out of 30 cases were primary MND. Out of 6 secondary MND, 4 cases were due to high lead levels, one due to high aluminium levels and one was due to paraneoplastic syndrome.
- 8 cases were ALS variant, 2 were of Madras MND variety and one was SMA variant. All secondary MND cases were of ALS variant
- Progression was rapid for secondary MND (within 9 months), cases with high lead levels had the fastest progression (mean of 6 months). Amongst primary MND, ALS variant progressed to death within the mean of 3.1 yrs and rest of the variants showed delayed progression as late as 20 yrs for SMA variant, 6yrs for PLS variant and between 5 to 10yrs (mean 8yrs) for Madras MND variant
- At onset, 18 cases started with lower limbs, 10 cases started with upper limbs and 2 cases had bulbar onset, bulbar onset had rapid progression (mean 5 months) and poor prognosis
- 27 patients had occupations involving high physical activities, 3 were of sedentary lifestyle. 6 of them had occupational exposure to heavy metals containing paints, solvents, glues and other chemicals
- Only 2 cases were born out of consanguineous marriage, probably had genetic aetiology, rest of the cases had a sporadic cause
- 11 cases had weakness as predominant symptom whereas 19 cases had wasting as predominant symptom. It was observed that cases who had delayed progression had wasting predominantly
- 24 cases had head and neck involvement and 18 had bulbar palsy and 6 had pseudobulbar palsy
- 6 cases had pure limbs involvement, 18 cases had limbs plus bulbar involvement, 6 cases had limb plus pseudobulbar involvement and no case had pure head and neck involvement
- Upon staging the severity of the disease as per King's clinical staging[8]:

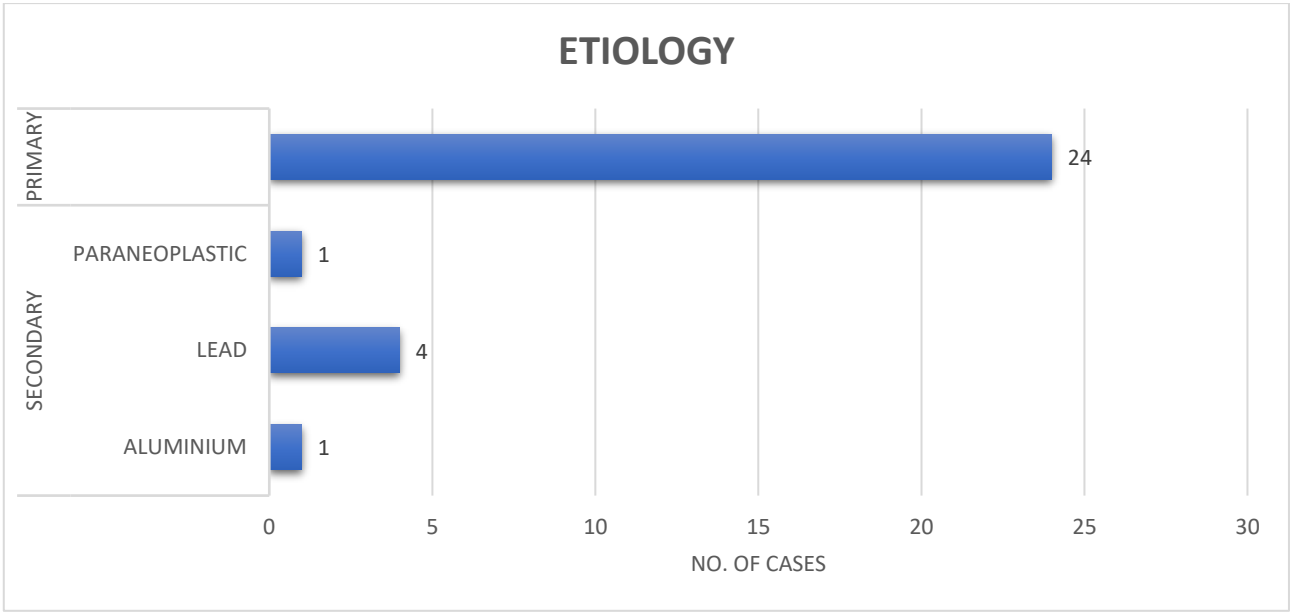
KING'S CLINICAL STAGING	NO. OF CASES
Stage 1 (1 clinical region)	0
Stage 2 (2 clinical regions)	5
Stage 3 (3 clinical regions)	1
Stage 4 (Nutritional/ Respiratory failure)	0
Stage 5 (Death)	24

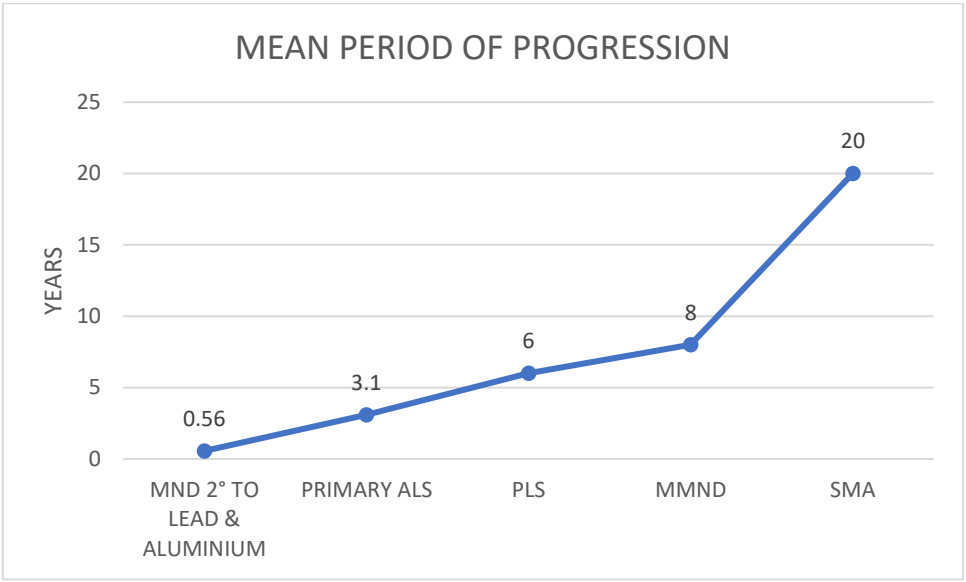
- Cause of death in these cases was either due to aspiration pneumonia (14 cases) or respiratory failure (9 cases) with aspiration pneumonia found to be more associated with bulbar palsy. Only one case was found to have died of liver failure (secondary to chronic alcoholism) i.e., cause other than MND
- Only 1 case showed bowel, bladder and EOM involvement which was suspected to be secondary to paraneoplastic aetiology
- All cases showed asymmetric quadriparesis, all had intact higher mental functions
- Only one case was found to be diabetic and hypertensive, rest of the cases had no comorbidities
- There was no significant association found between addictive habits and the disease

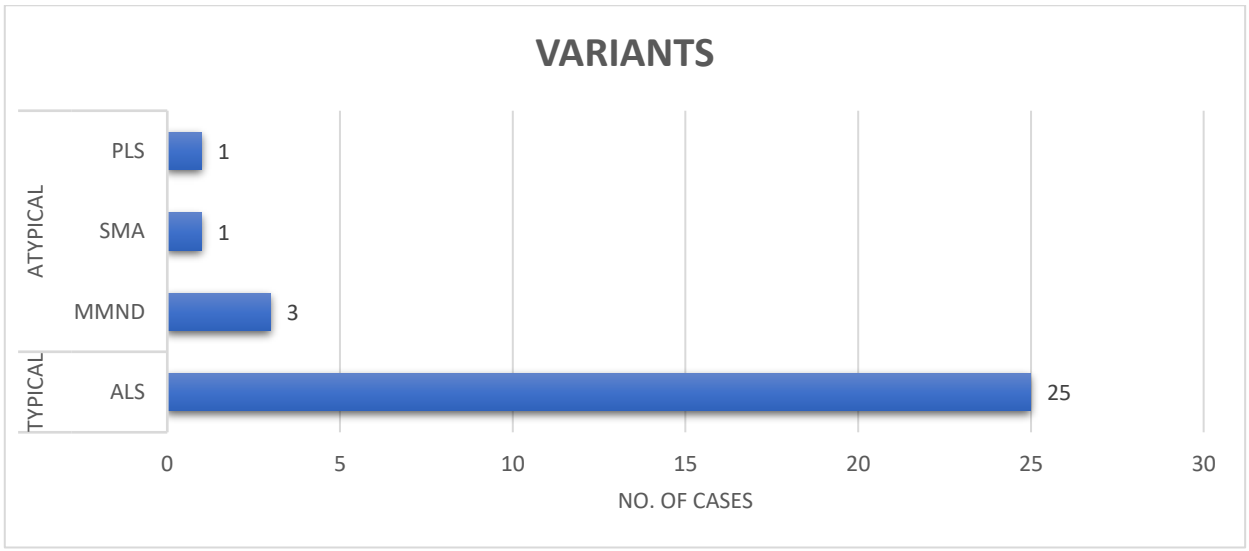


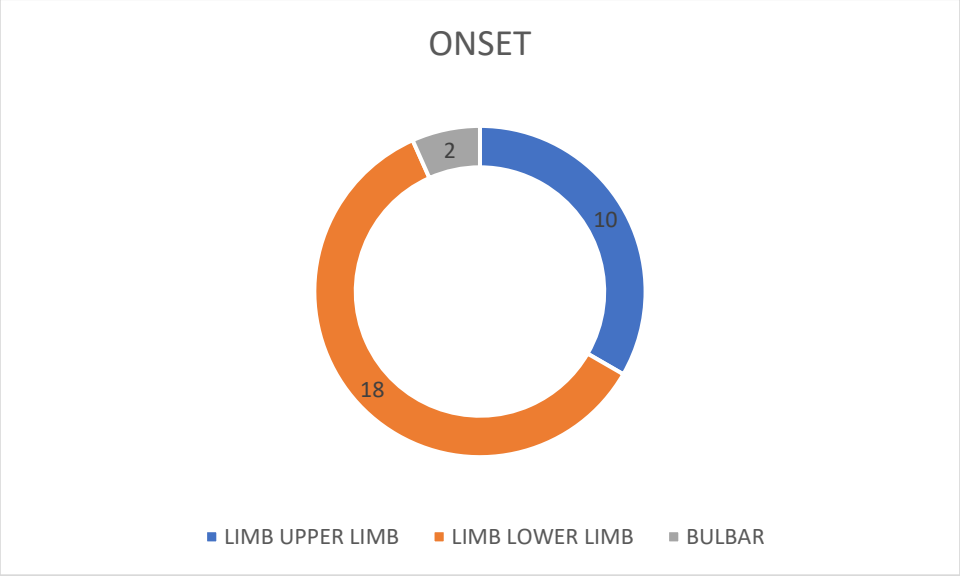

GENDER DISTRIBUTION
4
26
FEMALES
MALES

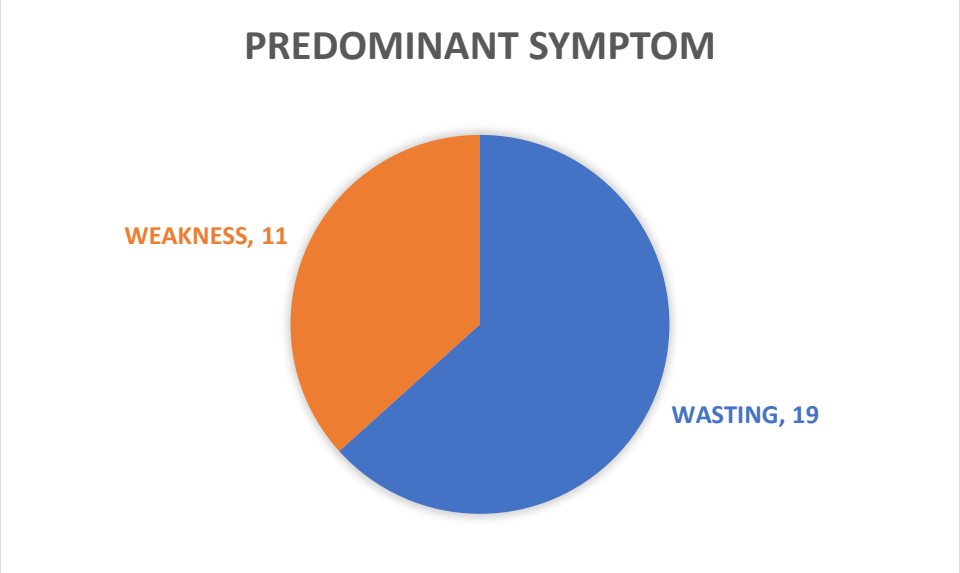

OCCUPATION
NO. OF CASES
10
9
8
7
6
5
4
3
2
1
0
9
5
1
7
1
1
2
1
1
1
1
FARMER
PAINT HANDLERS
CARPENTER
LABOURER
PLUMBER
CIVIL ENGINEER
HOUSE WIFE
ESTATE MANAGER
STUDENT
DOCTOR
BANK CLERK
PHYSICAL
SEDENTARY

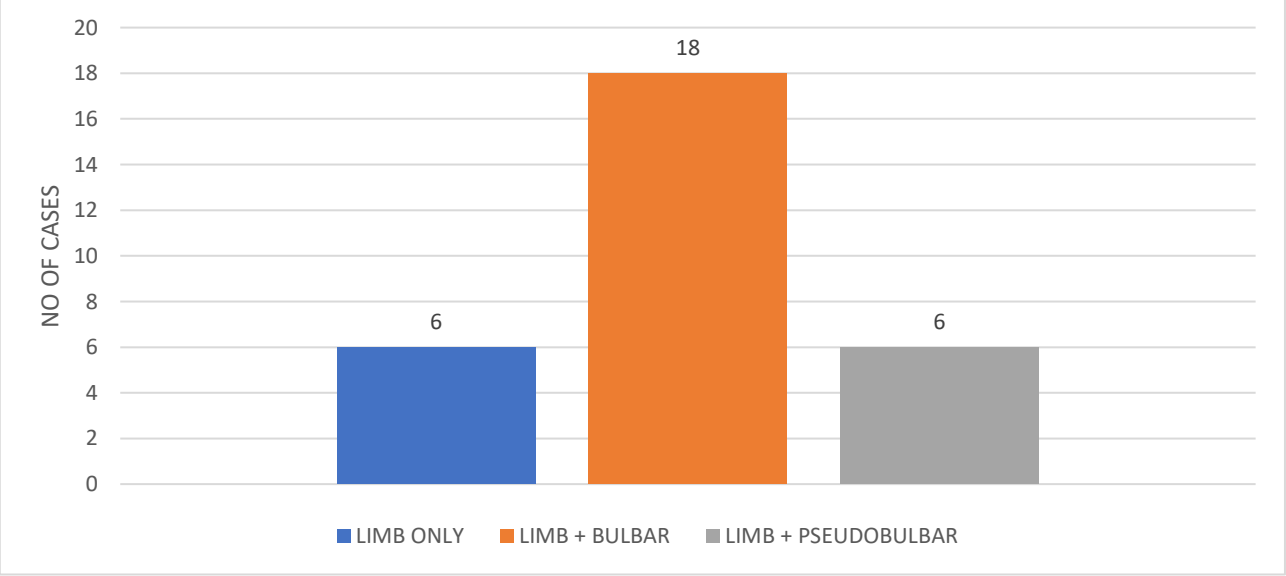

ETIOLOGY
PRIMARY
SECONDARY
PARANEOPLASTIC
LEAD
ALUMINIUM
24
1
4
1
0
5
10
15
20
25
30
NO. OF CASES

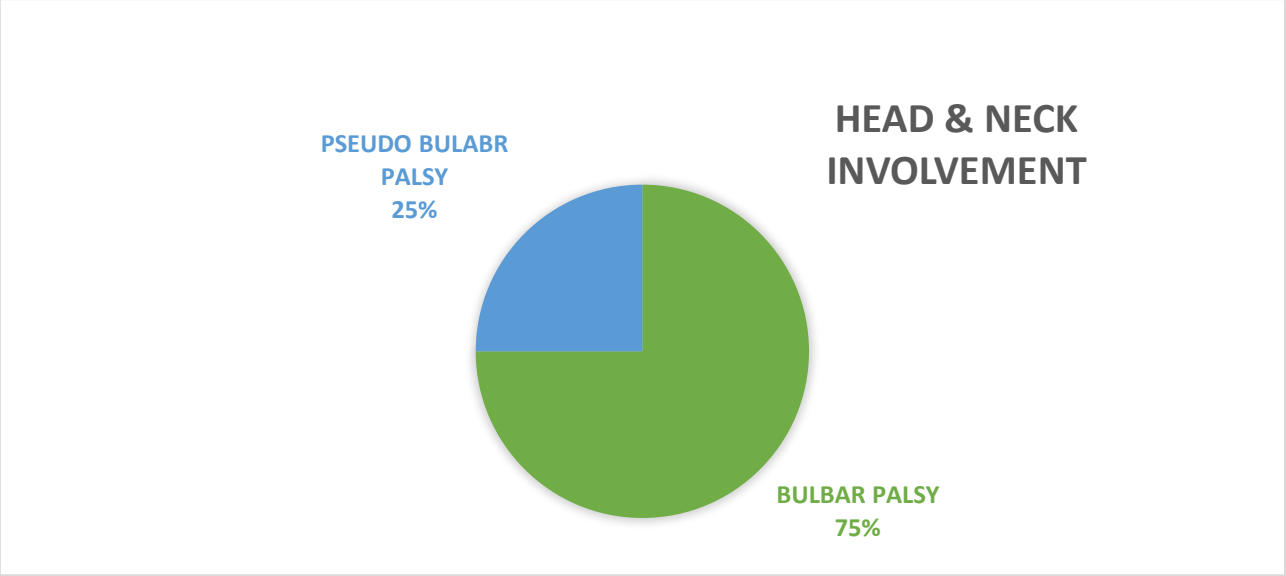

MEAN PERIOD OF PROGRESSION
YEARS
25
20
15
10
5
0
0.56
3.1
6
8
20
MND 2° TO LEAD & ALUMINIUM
PRIMARY ALS
PLS
MMND
SMA


VARIANTS
ATYPICAL
TYPICAL
PLS
SMA
MMND
ALS
1
1
3
25
0
5
10
15
20
25
30
NO. OF CASES


ONSET
2
10
18
LIMB UPPER LIMB
LIMB LOWER LIMB
BULBAR


PREDOMINANT SYMPTOM
WEAKNESS, 11
WASTING, 19


20
18
16
14
12
10
8
6
4
2
0
NO OF CASES
18
6
6
LIMB ONLY
LIMB + BULBAR
LIMB + PSEUDOBULBAR



DISCUSSION:

- All primary ALS had age of onset between 50 to 60 yrs., mean age of onset was 51.8 yrs. Studies show that the age of onset can be up to a decade earlier in Indian population[4]. The predominant group was sporadic form
- In this study we did not get any case with positive family history but 2 cases of ALS were born out of consanguineous marriage
- Madras MND was more common as expected in Southern India as per the past studies conducted in South India[6]
- This study shows high male preponderance in accordance to few western studies which showed male: female ratio of up to 20:1.[(3,4)]
- All cases which were suspected to be due to occupational exposure to toxins were found to have high toxin levels (lead/ aluminium) which also had earlier onset and faster progression of the disease. Since all these cases were brought in serious/ emergency state, interventions for the same could not be done effectively to conclude whether it slowed or halted the progression
- However other signs or other systemic effects of lead toxicity were not seen in these patients
- Earlier the onset of MND, better is the prognosis. SMA variant had early onset and better prognosis
- All patients with Madras MND variant were thin built and had slowest overall progression and best prognosis with no head and neck involvement. One case of MMND mimicked MMND variant where it had additional visual (optic atrophy) and auditory (sensorineural hearing loss) symptoms with lower cranial nerve nuclei involvement, in concordance with the previous large-scale studies on MMND[6]
- More than 90% of patients had occupations involving heavy physical activities reflecting that people with heavy physical activity are more prone to get MND[9]. Also, carpenters, house painters, factory workers were found to be at risk of developing MND in accordance to past studies[9] due to exposure to paints, glues, solvents containing heavy metals like lead and lead has direct toxic effect, inhibits axonal flow, inhibits neurotropic hormones and halts metabolism of neurons[9]. This study also proves the fact that bulbar onset of MND has poor prognosis and faster progression[4] but the tendency of bulbar onset being more common in older women was not observed in this study

- There was no relationship found between associated co morbidities or addictive habits like smoking/ alcoholism
- Females having high bulbar involvement[9] could not be established due to lack of adequate female cases
- Most consistent finding on neural imaging (MRI) was anterior horn cell sclerosis, few cases also showed sclerosis of lateral corticospinal tract
- Case 17 was a Doctor who had great knowledge about the nature of the disease, with best access to palliative care and was on regular follow up with neurologists from NIMHANS and recurrent in-time admissions for complications like aspiration and was resolved off all the emergencies for almost 10 yrs. He was on RT feeds even with intact cognition, had access to Robotic limb assist devices, bed sore prevention techniques, motorised wheel chair, DVT prophylaxis devices etc. This shows that better palliative care can vastly prolong the life span of patients and that there is still lot of potential in palliative care in MND cases which are the only proven ways that are known to reduce mortality
- Our Institute is a tertiary care center and hence patients come to us mostly on referral basis at a late stage of the disease course and a diagnosis of definite ALS is made in many patients before they visit our institute. Hence, the high proportion of definite ALS in the present study

- **LIMITATIONS:**
- Low sample size, limited to one tertiary care centre with short duration of study when compared low incidence of the disease
- No workup could be done to identify genetic aetiology
- Many cases of the ALS were brought in an emergency state where effective history, examination could not be elicited and investigations/ interventions could not be done
- This study was vulnerable to selection bias, recall bias, and potential non-standardised data collection.

CONCLUSIONS:

- Mortality rates in MND depends on type of MND and subtypes like Madras Motor Neuron disease has the slowest progression and best prognosis of all the subtypes
- Occupational exposure to chemicals, solvents, heavy metals is important to be elicited as early detection can lead to prompt treatment and that can halt the progression or probably reverse the symptoms, as this study shows that MND due to lead/ aluminum poisoning will show rapid progression and early onset
- The relative rarity of the disease makes it difficult to collect large, non-selected, population-based samples in order to carry out unbiased studies
- Inadequate sample size may have reduced the statistical power of the analysis. However, any study has constraints in terms of time and resources.
- Motor neuron disease remains a devastating illness, and although no breakthrough has been made in terms of a cure, we can offer patients various palliative interventions to enable longer survival with maintenance of independence and a good quality of life.

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