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Clinico-Electrophysiological Profile and Pattern of Anterior Horn Cell Diseases: A Prospective Study from Eastern India

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Abstract

Background: Anterior horn cell disease (AHD) refers to broad family of heterogeneous disorders that affect anterior horn cells of both childhood, adult and includes familial / sporadic or inflammatory/ immune disorders and others of undetermined case. Limited datas are available from eastern India despite disabling nature of the disease. Thus the present study is undertaken to evaluate clinical pattern, clinic-radiologic characteristics of AHD in eastern India and to find any factor which might be etiologically related. **Method:** This present study was conducted at Department of Neurology, S.C.B.Medical College &Hospital,Odisha a tertiary care centre in Eastern India. A total of 150 patients of anterior horn cell diseases 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 Study and electromyography (EMG) has been conducted on RMS Neuro machine at this center. **Results and Discussion:** Out of 150 cases studied Amyotrophic lateral sclerosis (ALS), Progressive muscular atrophy (PMA), Spinal muscular atrophy (SMA), Post-polio syndrome (PPS), Monomelic Amyotrophy (MMA) constituted 72(48%), 12(8%), 16(10.6%), 4(2.6%), 42(28%)cases respectively. Disease found to be more common in males except PPS variant where gender ratio found to be equal. Average duration of symptoms before presentation varies from 6 month - 3yr. Mean age of presentation found to be earlier in SMA (8.2yr) and MMA (22.5yr) and later (>40yrs) in rest patterns (ALS, PMA, PPS). Field and industrial working, h/o trauma or surgery were common environmental exposures in ALS, MMA subgroup of this cohort study. Familial associations found in SMA(6,31%) and MMA(1,2.4%) subgroups only .Limb onset were seen in117(78%) cases and Bulbar onset in 14(9.3%) cases. Neurogenic pattern of EMG seen in all subtypes of AHC diseases.MRI spine showed degenerative changes of cord in 15(10%) cases. Focal cord atrophy was found only in MMA in 3(2%) cases. **Conclusion:** ALS, MMA were common variant of AHD. Age of onset was later in ALS (>40yr) & PMA (>60yr). Familial association though rare, found in SMA, MMA group. Weakness &wasting were characteristic features in

all types of AHD. Onset of Limb involvement was a major presentation in this study. Bulbar symptoms/signs found in ALS, PMA variety. Monomelic amyotrophy, a special variety of AHD found to be not rare in this part of India. Neurogenic EMG found in all variant AHD.

Keywords: Anterior horn cell, Motor neuron disease, Amyotrophic lateral sclerosis, Spinal muscular atrophy, Post-polio syndrome.

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Introduction

Anterior horn cell disease (AHD) are referred to broad heterogeneous family of disorders that affects ant. horn cells (LMN Neurons), which includes familial/ sporadic disorders, inflammatory/ immune disorders and others of undetermined case.[1] Motor neuron disease(MND) is a broad clinical spectrum of motor neuronopathy that affect the upper motor neuron (UMN) and / or lower motor neuron.[2] Many of the MNDs are diffuse, sporadic and progressive , however, some of them are hereditary.[3] or focal.[4] Amyotrophic Lateral Sclerosis(ALS) is most common MND in adults and spinal muscular atrophy (SMA) is most common in children.[5,6]

Some forms of MNDs selectively affect upper motor neuron (Primary lateral sclerosis), some selectively affect lower motor neurons (Spinal muscular atrophy) and in some both upper & lower motor neurons affected simultaneously (ALS).[7]

UMN features are paresis, spasticity, spastic dysarthria, pseudobulbar palsy, hyperreflexia and /or presence of pathological reflexes.[8]

LMN feature on the other hand cause paresis, atrophy, hypo reflexia or areflexia or cramps and fasciculations.[8]

Nerve conduction study (NCS) features are decrease amplitude of compound muscle action potential (CMAP) with normal sensory nerve conduction study. EMG characteristics of AHD are features of acute denervation (fasciculations, fibrillation potential, positive sharp waves, increased insertional activity, and delayed recruitment) & features of chronic reinnervation (broad, high amplitude, polyphasic motor unit potentials). Importance of Magnetic resonance imaging (MRI) of spine in AHD is to find degenerations in some cases and to exclude compressive lesions of cord.

Clinical studies on the pattern of MND in north, west and south India are well established but few report is available from eastern India.[9-12]The present study was undertaken to determine the clinical pattern, Clinico-Electrophysiological characteristics of AHD & to find any factor which might be etiologically related.

Diagnostic criteria's used for different variety of AHDs are as follows.[13]

ALS

1. UMN plus LMN signs in three regions.
2. Progressive disorder.
3. Absence of sensory sign, sphincter disturbance, dementia, extrapyramidal feature, autonomic, ysfunction and compressive myelopathy.
4. Neurogenic change in EMG with normal motor and sensory nerve conduction velocity.

SMA

1. LMN signs in limbs (predominantly proximal involvement) or bulbar muscle.
2. Slowly progressive disorder.
3. Early age of onset.
4. Absence of involvement of peripheral nerve or long tract.
5. Family history may or may not be present.
6. EMG evidence of anterior horn cell disorder with normal nerve conduction.

PMA

1. LMN signs in limbs (predominantly distal).
2. Progressive disorder.
3. Relatively later age of onset.
4. Absence of involvement of peripheral nerve or long tract.
5. EMG evidence of anterior horn cell disease with normal nerve conduction.

Monomelic amyotrophy (MMA)

1. Wasting and weakness usually restricted to a single upper or lower limb.
2. Occurrence in young male.
3. Very slow course.
4. Evidence of LMN involvement of limb.
5. Bulbar cranial nerves, cerebellar, extra pyramidal, pyramidal and sensory system are spared.

EMG evidence of anterior horn cell disease

1. Increased insertional activity.
2. Presence of resting activity in the form of fibrillation and fasciculation in muscles of lower and upper extremity.
3. On volition, increase in amplitude and duration of motor unit action potential (MUP) with polyphasicity and reduced interference pattern.
4. Normal electrical excitability of both motor and sensory nerve.
5. Conduction velocity is normal in sensory nerves and not less than 70% of the normal average value according to age in motor nerves.

Materials and Methods

This prospective study is done at department of Neurology of S.C.B. Medical College and Hospital, Cuttack, Odisha, a premier Institute of eastern India, during period from October 2017 to November 2019. In this present study we described clinical pattern, clinico-electrophysiological profile of various types of Anterior cell Diseases. Clearance from institutional Ethical Committe obtained prior the study. (IEC/IRB No:901/14.10.19, Odisha)

Study Population

Patients presenting to neurology OPD / IPD of S.C.B.Medical college & hospital,a tertiary care center of eastern India who fulfills below criteria's were enrolled for study.

Inclusion Criteria's

1. Patients of all age groups with features of anterior horn cell involvement.
2. Patients with pure LMN signs with or without UMN signs in at least one segment (bulbar/cervical/thoracic/lumbosacral)were included.
3. Patients with above clinical diagnosis supported by electophysiological parameters included.

Exclusion Criteria's

1. Patients found to have alternate diagnosis or structural abnormality after undergoing radiological or other investigation.
2. Patients diagnosed before study period.
3. Patients do not give consent Standard criteria above were used to assign specific diagnosis to each group. Informed consent has been taken from all patients included in study.

Study tool

The study tools were Neurological instruments for clinical examinations, RMS Nerve conduction test machine and EMG needle & RMS EMG machine for investigation.

Data Collection

Pre-designed proforma was used to record information from individual patients. All patients were subjected to detailed history, examinations (general and neurological) & investigations. Proforma was filled with headings of age of presentation, duration of disease before presentation, sex ratio, family preponderance, environmental factors, clinical pattern of involvements (onset pattern,

weakness, atrophy, fasciculations, cranial N. involvement, deep tendon reflexes).

Investigation

Routine haematological, biochemical parameters (FBS, PPBS, Thyroid profile, Renal function test) and other investigations like ESR, Serum Vit B12, Xray chest PA view, USG abdomen & pelvis were done in each case. In selected cases collagen profile, serum CPK level, Serum electrophoresis were done. 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 digitiminimi 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 were evaluated on the affected side. For the paraspinal thoracic muscles, the patient was asked to lie prone, with a soft cushion under the abdomen and to relax then head, shoulders and arms towards the ?oor. EMG of ant. horn cell diseases showed features of Acute denervation (fasciculations, fibrillation potential, positive sharp waves, Increased insertional activity , delayed recruitment), and features of chronic reinnervation are broad, high amplitude, polyphasic motor unit potentials. All cases were subjected to 1.5 tesla MRI seen of cervical spine, Lumbar Spine or brain as per symptoms.

Statistical Analysis

All the data put in prescribed format were analyzed using SPSS software Version 21. The descriptive statistics of the study population were reported as count and percentage for categorical variables and mean±standard deviation for continuous variables with normal distribution.

Results

A total 150 Patients were enrolled. The different types of AHDs in our Institution are shown in Table-1, which revealed that commonest variety is ALS(48 %) and MMA(10.6%) constitutes a seizeable proportion.

Table 1: Age of onset and sex ratio

Gourie Devi etal		Chopra etal	Bharucha etal	Wadia etal	Saha etal	Debasish etal
Total	323 (100%)	124 (100%)	82	401 (100%)	110 (100%)	150 (100%)
ALS	124 (38.4%)	61 (49%)	29 (35.4%)	183 (34.4%)	48 (43.6%)	72 48%)
SMA	110 (34.1%)			51 (12.7%)	22 (20%)	42 28%)
MMA	27 (8.3%)	62 (50%)		54 (13.4%)	25 (22.7%)	16 (10.6%)
PMS	48 (14.9%)	1 (0.8%)	58 (64.6%)		12 (10.9%)	12 (81%)
PPS					2 (1.8%)	4 (2.41%)

Madras MND					1 (0.9%)	

Male is to Female ratio was 2.6:1 in AHD except PPS variety where M:F remains 1:1(Table-2).Age of onset was later in ALS & PMA(≥4th decade) while it was earlier in SMA (1st, 2nd decade) & MMA (2nd ,3rd decade) (Table-2).

Table 2: Age of onset and Gender distribution

Age of onset and Gender distribution						
Decades	ALS(n=76)	PMA(n=12)	SMA(n=16)	PPS(n=4)	MMA(n=42)	Total(n=150)
1st	0	0	12(75%)	0	0	12(8%)
2nd	0	0	2(12.5%)	0	24(57.1%)	26(17.3%)
3rd	0	0	2(12.5%)	0	18(42.9%)	20(13.3%)
4th	4(5.3%)	0	0	2(50%)	0	6(4%)
5th	4(5.3%)	0	0	2(50%)	0	6(4%)
6th	43(56.57%)	3(25%)	0	0	0	46(30.7%)
7th	25(34.9%)	9(75%)	0	0	0	34(22.67%)
M:F	52:24(2.1:1)	7:5(1.4:1)	10:6(1.6:1)	2:2(1:1)	38:4(9.5:1)	109:41(2.6:1)

Mean age of presentation was later in PMA (54.8 yr) & ALS (51.8yr) and earlier in SMA (8.2yr)& MMA(22.5yr)(Table-3). Familial association though not remarkable, found in SMA, MMA variants. (Table-3).

Table 3: Clinical data

Sub types of AHC diseases	Mean age at present action	Pasitive Family history	UL involvement	LL involvement	Bulbar involvement	Mills hemiplegic variant	Flickering sensation	Cranial Nerve involvement			Deep tenden reflexes			Plantar reflex
								7th	9th, 10th	12th	Normal	Decreased	Increased	
ALS N=72 (100 %)	51.8yrs	0	39 (57.3%)	21 (27.6%)	13 (17.1%)	3 (3.9 %)	59 (77.63 %)	3 (3.9 %)	32 (42.1 %)	46 (60.5 %)		2 (2.7%)	70 (97.2%)	72 (100%) (Extensor)
PMA n=12 (100 %)	54.8yr	0	6 (50%)	5 (41.67%)	1 (8.23%)	0	1 (8.3%)	0	1 (8.3%)	1 (8.3%)		12 (100%)		12 (100%) Flex or
PPS n=4 (100 %)	42.3yr	0	1 (25%)	3 (75%)	0	0	2 (50%)	0	0	0		4 (100%)		Flexor 4 (100%)
SMA n=16 (100 %)	8.2yr	5 (31.2 %)	16 (100%)	16 (100%)	0	0	5 (23.8%)	0	3 (18.7 %)	0	3 (18.25	13 (81.25 %)		Flexor 16 (100%)
MMA n=42 (100 %)	22.5yr	1 (2.4%)	39 (92.9%)	3 (7.1%)	0	0	10 (23.8%)	0	0	0	14 (33.3 %)	24 (31.58 %)	4 (9.5%)	Flexor 42 (100%)
Total n=150 (100 %)		6 (4%)	85 (56.6%)	32 (21.3%)	14 (9.3%)	3 (2%)	84 (56%)	3 (2%)	47 (24%)	47 (31.3 %)	17 (11.3 %)	55 (36.6%)	74 (49.3%)	

Majority variety did not shown any kind of environmental exposure even though Field or industry worker(16%), h/o trauma or surgery(18.7%) and drug or alcohol abuse(12%) were common environmental factors found (Table-4).

Table 4: Exposure of Environmental Factors

Sub type	h/o trauma or Surgery	Drug or Alcohol abuse	Field or Industry worker	None
ALS	12(15.8%)	15(19.7%)	17(22.4%)	40(52.1%)
PMA	2(16.7%)	2(16.7%)	2(16.7%)	7(58.3%)
PPS	1(25%)	0	0	3(75%)
SMA	0	0	1(6.3%	15(93.8%)
MMA	9(21.4%)	1(2.4%)	8(19%)	28(66.07%)
Total	24(16%)	18(12%)	28(18.7%)	93(62.1%)

Most of subgroups of AHD present within 1yr or 1-2yr of onset of disease where as PMA, PPS present beyond 2yr (Table-5).

Table 5: Duration of disease at Presentation

Sub type	<1yr	1-2yr	>2yr	Total
ALS	24(31.6%)	34(44.7%)	18(23.7%)	76(100%)
PMA	0	0	12(100%)	12(100%)
SMA	6(37.5%)	7(43.75)	3(18.75%)	16(100%)
PPS	0	0	4(100%)	4(100%)
MMA	52(52.4%)	11(26.2%)	9(21.5%)	42(100%)

Flickering sensation was seen in 84(56%) cases among whom tongue fasciculation most common .Limb onset of weakness ,wasting was present in this study in 117(77.9%) cases & Bulbar onset in form of dysphagia, slurred speech, nasal regurgitation ,tongue atrophy & fasciculation present in 14 (9.3%) cases[Table-3]. Deep tendon reflexes (DTR) were decreased in most variety. In ALS Deep tendon reflexes were increased in 70(97.2%) cases [Table-3]. No sensory abnormality seen in any case.

Nerve conduction study(NCS) was normal in 88(58.7%) cases[Table-6].Denervation EMG with fibrillation and fasciculation potentials (Prominent in tongue, limb muscles) were abnormalities seen in various segments(bulbar, cervical, thoracic, lumbo-sacral). Denervation EMG present in four limbs in 40(52.6%) cases with spontaneous activity in 66 (86.8%) cases in ALS whereas all denervation findings were restricted to one segment in 37(88%)cases in MMA [Table No.-6].

Discussion

Incidence of MND in India varies from 0.06% to 0.11% of all neurological diseases presented to outpatient department as recorded from various studies in different parts of the country like Chopra etal.[9] from North India, Bharucha etal.[10] from west India, Wadia etal.[11] from Central india, Saha etal from east india[13]&Gouriel Devi etal at South india[12] .Prevalence of MND Varies from 2.86 per 100000 in rural Bengal (Study by Das et al)[14] to 4 per 100000 population in Bangalore (Study conducted by Gouris Devi etal)[12]. The incidence variations in different studies were due to

different sources of data collection and sample population studied.

In our study ALS variety constitutes majority bulk followed by MMA& SMA. PPS constitutes least common variety of AHD. This pattern of AHD in our study is similar to other Indian studies.[11,13] [Table-1]. Increased incidence of MMA cases in our study is accordance to Chopra etal can be explained due to more awareness about this entity and young age of affection. The present study shows male dominance (2.6:1) which is similar to other indian studies.[7,13] Review of Western Literatures shown male predominance ranging from 1.2:1 to 20:1, although some literatures shown, no sex difference.[15] or even female dominance.[16] On subgroup analyses M:F ratio were 2.1:1, 9.5:1 in ALS & MMA which is similar to Indian study by Gourie Devi et al.[12] Study by Saha etal13 Shown higher sex ratio. No gender difference in PPS group found in this study.

Age of onset on analysis found to be later in ALS(≥4 decade) &PMA(≥6decade) and earlier in MMA(2nd,3rd decade) &SMA(1st,2nd,3rd decade). In study by Gourie Devi etal mean age of onset for ALS and MMA were 46.2±14.1% yr (18-85yr) and 19.5±4.18yr, which is concordant with our study. The age of onset of ALS in our study found to be 4th to 7th decade which is lower than western studies.[17,18] It is to be noted that mean age of onset MND in India is one decade earlier than western countries.[7] This may be explained by larger young populations in our country. In our cohort mean age of onset of MMA is 22.5year ,which is at par with other Indian studies[Gourie devi etal, Ranvir yadav etal.[19]

In the present study, age of onset in PPS group was 4th,5th decade & mean age at presentation was 42.3yr which is similar to study by BANG etal[20] where as ,majority polio survivors were middle aged and mean age of presentation was 51.2 ± 8.3yr. All the findings agreed that Indians appears to have a relatively younger age of onset and prolonged survival suggesting relatively slow progression of ALS among Indian patients.

Duration of disease at presentation for PMA,PPS were>2yr, while in other variants it was mostly <2yrs.This is dissimilar to study by saha etal where majority MMA present beyond 2yrs. The earlier presentation of MMA in our study may be due to young age of onset and more awareness about symptoms like weakness, thinning of limbs. Later presentation in other subgroup may be due to low literacy rate, poverty, less awareness about health ailments.

Familial clustering is seen in SMA group mainly which is discordant with other Indian studies.[7,13] In one study conducted by Leigh and Roychaudhuri autosomal dominant inheritance reported in 5-10% of patients from ALS.[21]

In the present study h/o field / Industrial work or h/o trauma/ surgery or h/o drug/alcohol abuse were present in ALS,PMA & MMA. Associations of h/o trauma/ surgery was only found in PPS variant. Similar findings noted by many literatures from india.[7,13,22] Mechanical injury as a risk factor for MND was significant and demonstrated by Kondo and Tsubaki from Japan.[22],Gourie Devi.[12] & Saha etal.[13] from India. Another observation seen by Gourie Devi etal & Saha etal is prior history of electrocution, surgery but no correlation was found between initial manifestation of MND and site of trauma or electrocution . Hence it necessitates taking detail history .

Flickering or twitching of muscle were present in ALS (77.63%),PMA(66.7%) , SMA(31.3%), PPS(50%), MMA(62.7%) sub types of AHD which is dissimilar to study by Shah etal.[13] where twitching or fasciculations were found in less number. Interestingly patients of MMA

subgroup had no fasciculations.[12] Study by Chopra etal shown fasciculations in 82.1% of ALS. This greater incidence of fasciculations may be due to literacy and greater emphasis on history of fasciculations or twitching

Weakness & wasting of muscles were found in more than 80% patients of all subgroups in present study which is comparable to other Indian studies.[7,9-13]

A study by sachin et al.[23] shown Limb onset & bulbar onset of MND in 72% & 28%cases respectively,nearly similar to our study. Another Indian study by saha etal shown various onset pattern of MND as Limb onset(43.7%),Bulbar onset(6.5%),Pseudobulbar onset(4.1%),Limb+bulbar onset(33.3%). So our onset pattern of ALS is accordance with above Indian studies. Gourie Devi etal.[12] in her study of MMA shown brachial, crural onset as 80%, 19.72% where as in our study brachial, crural involvements were 92.9%, 7.1%. Less no. of crural onset in our study may be due to less sample size.

Cranial nerve involvement seen mostly in ALS variants in our cohort, which was in conformity with study by Gourie Devi etal.[12] But Saha etal shown Cranial nerve involvements in ALS only, with one case of 2nd cranial nerve involvement which has been not reported before .All above studies confirmed 12th Cr. Nerve as commonest affected nerve.[12,13]

Emotional incontinence, a feature of ALS was present in 42.1% cases in present study which is higher than other studies.[13,24] This may be due to later age of presentation with advanced disease resulting pseudobulbar effect.

Sensory symptoms like cramps , needles, pins were encountered without any sensory signs by saha etal where as no sensory signs or symptoms were present in any variant in our study.

The striking feature of MMA variant in present study, is wasting & weakness restricted to either single upper limb or lower limb, male dominance, slow course and lack of involvement of other parts of Central or Peripheral nervous system. This type constituted 22.7% of the series of saha etal.

Involvement of single lower limb is reported as Wasted leg syndrome by prabhakar etal.[25]

Another characteristic variety of AHD not found in our study is Madras variety MND, reported from Tamilnadu, southernmost state by Jagannath etal.[26] Gourie Devi etal in her study reported 3.7% cases of Madras variety MND.

Nerve conduction did not reveal any abnormality except decrease amplitude of compound motor action potential(CMAP) in motor nerve conduction. EMG features were neurogenic in all varieties of AHD[Table-6]. Features were acute denervation with presence of fibrillation & positive sharp waves was present in 42.9%-86.8% patients. Chronic denervation in various segments were present in all patients. None of our patient had shown myogenic EMG even though Saha etal shown in their study presence of neurogenic, myogenic & mixed EMG features.[13] This concludes that all our patients were in slowly progressive stage.

In study by saha etal cervical disc degeneration , focal cord atrophy in ALS were found in 6,1 cases respectively out of 8 cases undergone imaging where as study by Gourie Devi etal shown asymmetrical lower cord focal atrophy in 44.6%cases of MMA. Focal cord atrophy was observed in 3(7.1%) cases in our study. Decrease incidence of focal cord atrophy in MMA group in this study may be due to less sample size in our study.

LIMITATIONS

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

Conclusions

This study has been conducted at Sriram Chandra Bhanj medical college & Hospital ,a tertiary care center of Odisha. ALS found to be commonest variant AHD and MMA is found to be of higher frequency relative to other Indian studies. Earlier age of onset is the feature of MMA & SMA. Male dominance is found in all variants except PPS where no gender difference found. Duration of the disease at presentation is more than 2years in PMS,PPA subtypes while in others it is varied. Familial clustering though rare seen only in SMA, MMA variants. No definite relation with occupation is found in the present study. Prior h/o trauma or surgery, drugor alcohol abuse, field or industrial working may be casually related to ALS, MMA, PMA variant. Bulbar symptoms/signs are characteristic features in ALS, PMA and absent in other variants of AHD. Wasting , weakness & cranial nerve affection are characteristic features of ALS. Neurogenic pattern with acute and chronic denervation is key EMG feature . Neurogenic pattern EMG also seen in unaffected homologous limb in MMA. Focal cord atrophy is the only MRI feature present in MMA.

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