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### RESEARCH ARTICLE

## CLINICAL PROFILE OF MOTOR NEURON DISEASE IN KASHMIR VALLEY – A HOSPITAL BASED STUDY.

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#### Abstract

**Background:**-This general term is used to designate a progressive degenerative disorder of motor neurons in the spinal cord, brainstem and motor cortex, manifesting clinically by muscular weakness, atrophy and corticospinal tract signs in varying combinations. There is no report on clinical profile of motor neuron disease or amyotrophic lateral sclerosis (ALS) from the state of Jammu and Kashmir.

**Objective:** To find the clinical profile of motor neuron disease in Kashmir valley.

**Methodology:**-This hospital based study was conducted on 40 patients of motor neuron disease (MND) visiting OPD / IPD of Department of Medicine, SMHS Hospital. Patients were studied for their presentation, etiology, clinical and laboratory features.

**Results:**-Majority of our patients i.e. 18 (45%) were falling in the age group of 51 to 60 years with males more than females with a male to female ratio of 1.85:1. Weakness of muscles was the most common presenting symptom in our patients with fasciculation as the most common motor system findings.

**Conclusion:**-Motor neuron disorders appear to be a clinically heterogeneous disorder with varied clinical presentation encompassing a range of upper or lower motor neuron dysfunction or both. The patients from Kashmir had disease onset earlier by a decade than most of the studies.

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#### Introduction:-

This general term is used to designate a progressive degenerative disorder of motor neurons in the spinal cord, brainstem and motor cortex, manifesting clinically by muscular weakness, atrophy and corticospinal tract signs in varying combinations.<sup>1</sup>

Upper motor neuron (UMN) is a motor neuron, the cell body of which lies within the motor cortex of the cerebrum and the axon of which form the corticospinal and corticobulbar tracts.

Lower motor neuron (LMN) – located in the brainstem and spinal cord and send out motor axons that directly innervate skeletal muscle fibres. Spinal cord LMN are also called as anterior horn cells.

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Motor neuron disease (MND) encompasses a group of rapidly progressive and universally fatal neurodegenerative disorders of the human motor system. Amyotrophic lateral sclerosis (ALS) is the commonest MND phenotype.<sup>2</sup>

#### **Diagnostic Categories:-**

Clinically definite ALS is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions.

Clinically probable ALS is defined on clinical or electrophysiological evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.

Clinically possible ALS is defined when clinical or electro-physiological signs of UMN and LMN dysfunction are found in only one region, or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have been performed and other diagnosis must have been excluded.

#### **Probable Laboratory Supported ALS**

1. Clinical evidence of upper motor neuron and lower motor neuron signs in only one region, or
2. Upper motor neuron signs alone in one region and lower motor neuron signs defined by EMG criteria in at least 2 muscles of different root and nerve origin in two limbs.

#### **Laboratory Evidence of UMN Involvement:-**

A number of promising imaging and electrophysiological techniques are being used in research studies as potential markers of UMN involvement.

#### **MRI:-**

Sometimes shows abnormal signal intensity in the corticospinal and corticobulbar tracts as they descend from the motor strip via the internal capsule to the cerebral peduncles.

The MR images have showed T<sub>2</sub> shortening in precentral cortices.<sup>3</sup>

#### **Diffusion Tensor MRI (DT-MRI):-**

It is a quantitative MRI imaging. It allows measurement of quantities reflecting the size such as Apparent Diffusion Coefficient (ADC) and orientation such as Fractional Anisotropy (FA) of water filled spaces in biological tissues. Compared to controls ALS patients have significantly lower FA in posterior limb of internal capsule, cerebral peduncle, corticospinal and cortico-bulbar tracts. ADC values were inversely correlated with the disease severity.<sup>4</sup>

#### **MRS (proton density – MRS):-**

Combines advantages of MRI with micro-biochemical information. In ALS patients with UMN signs, there is relative reduction of N-Acetylaspartate as compared to creatinine or choline (used as internal standards) in the sensorimotor cortex.

#### **TMS (Transcranial Magnetic Stimulation):-**

An electrophysiological technique used to detect cortical hyperexcitability/impaired inhibition as well as cortical motor neuron and long tract degeneration in ALS. There is increased central motor conduction time, increased absolute latency to a tested muscle. In patients with bulbar onset disease, a absent response to TMS in a limb is supportive of UMN lesion.<sup>5</sup>

#### **Laboratory Evidence of LMN Involvement:-**

World Federation of Neurology has laid down electrodiagnostic criteria for LMN degeneration.

Signs of active denervation<sup>6</sup>

Fibrillations

Positive waves

Signs of chronic partial denervation

Motor unit potential with increased duration

Frequent polyphasia with instability

High amplitude

Reduced recruitment except in the presence of significant UMN dysfunction.

#### **Aims And Objectives:-**

To find the clinical profile of motor neuron disease in Kashmir valley – A hospital based study.

#### **Materials And Methods:-**

The study entitled “Clinical Profile of Motor Neuron Disease in Kashmir Valley” was a hospital based prospective study, conducted in the Postgraduate Department of Medicine, SMHS Hospital, an associated hospital of Government Medical College, Srinagar. Forty (40) patients diagnosed clinically and by using El-Escorial Spain, the World Federation of Neurology established diagnostic criteria for ALS modified at Airline House Virginia in 1998<sup>7</sup> of MND visiting OPD / IPD of Department of Medicine, SMHS Hospital were included for the study.

#### **Exclusion Criteria:-**

1. Predominant cognitive impairment
2. Predominant bowel and bladder involvement
3. Predominant autonomic nervous system dysfunction
4. Predominant sensory impairment
5. Structural lesion on neuroimaging (CT/MRI)

Patients were evaluated and assessed for the following: (i) Gender, (ii) Age of onset, (iii) Pattern of onset, (iv) Presenting symptoms, (v) Cranial nerve involvement, (vi) Motor system involvement, (vii) Any environmental exposure to prior infection, toxins, surgery, trauma and radiation.

Investigations in each case included serum urea, serum creatinine, serum electrolytes, x-ray chest, blood sugar, MRI brain and spine and electromyography (EMG). EMG was performed in at least three limbs with Medelec Synergy EMG machine. In addition following tests were done in selected cases like cerebrospinal fluid analysis (CSF), thyroid profile, serum electrophoresis, serum calcium, ANA, CPK, HIV serology, muscle biopsy, nerve conduction studies to rule out other relevant disorders.

The diagnosis of MND was based on clinical findings of a progressive pure motor disorder with muscle weakness, atrophy and fasciculations in the absence of sensory deficit, cognitive impairment and sphincter disturbances. When the above findings were accompanying pyramidal signs, and the modified El-Escorial criteria proposed by World Federation of Neurology was met, a diagnosis of Amyotrophic Lateral Sclerosis was made.

The diagnosis of amyotrophic lateral sclerosis requires:-

The presence of Evidence of lower motor neuron degeneration by clinical, electrophysiological or neuropathological examination. Evidence of upper motor neuron degeneration by clinical examination; and

Progressive spread of symptoms or signs within a region or to other regions, as determined by history, physical examination or electrophysiological tests.

The absence of Electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/ or UMN degeneration, and Neuroimaging evidence of other disease processes that might explain the observed clinical and electro-physiological signs.

#### **Statistical Analysis:-**

The data obtained was carefully scrutinized, categorized, coded and statistically analyzed through software package SPSS 16.0 Version. The results were considered significant at p-value <0.05.

#### **Results:-**

Majority of the cases i.e. 18 (45%) were falling in the age group of 51 to 60 years followed by 10 (25%) in the age group of 61 to 70 years. There was male predominance over female with 26 (65%) and 14 (35%) male with a male to female ratio of 1.85:1. Weakness of muscles was the most common presenting symptom with 30 (75%) of patients followed by wasting of muscles 28 (70%). Fasciculation was commonest motor system findings with 36

(90%) followed by decreased power 34 (80%). XII cranial nerve was the most common nerve affected [24 (60%) of patients]. Cranial nerves (I-VIII) were intact in all cases. Limb onset pattern was more common than bulbar onset 26 (65%) and 14 (35%) respectively. Out of 26 (65%) patients with limb onset pattern upper limb onset was seen in 16 (61.44%) of patients. 28 (70%) patients were smokers, 4 (10%) had prior history of trauma, none of our patient had any exposure to toxins or radiation.

There were 18 (45%) farmers in our study, followed by 16 (40%) labourers with 12 (30%) housewives. 12 (30%) patients had hyperintense signals in corticospinal tract areas on MRI with 24 (60%) normal findings.

**Table 1:-** Age and Gender Wise Distribution of the Studied Subjects

Age Group (Years)	Male		Female	
	No.	%	No.	%
< 30	0	0	0	0
31-40	3	7.5	1	2.5
41-50	4	10	2	5
51-60	12	30	6	15
61-70	4	10	6	15
> 70	1	2.5	1	2.5

**Table :-2**

		No. of Patients	Percentage
<b>Symptoms</b>	Weakness of muscles	30	75
	Wasting of muscles	28	70
	Twitching	26	65
	Difficulty in speech	14	35
	Stiffness of limbs	18	45
	Dysphagia	4	10
	Emotional Lability	8	20
<b>Motor System</b>	Fasciculation's	36	90
	Decreased power	34	85
	Decreased Bulk	32	80
	Decreased tone	32	80
	Spasticity	24	60
<b>Cranial Nerve Involvement</b>	IX	8	20%
	X	8	20%
	XI	6	15
	XII	24	60

**Table :-3**

		No. of Patients	Percentage
<b>Pattern of Onset</b>	Limb	26	65
	Bulbar	14	35
<b>Pattern of Onset Among Limb Onset</b>	Upper limb onset	16	61.44
	Lower limb onset	7	26.92
	Monomelic	1	3.8
	Paraparetic	1	3.8
	Flail arm	1	3.8
<b>MRI Brain Findings</b>	Normal Study	24	60
	Hyperintensities in corticospinal tract area	12	30
	Cerebral atrophy	4	10

**Table 4:-**Result of the Investigations done as a workup for secondary causes of MND

	No.	%	Results	
TSH	16	40	Normal	
Serum CPK	8	20	Normal	
Serum Calcium	10	25	Normal	
HIV	10	25	Negative	
ANA	10	25	Negative	
Serum electrophoresis	6	15	Normal	
Nerve conduction studies	12	30	Normal	
CSF Analysis	Proteins	22	55	Normal
	Cells	22	55	Normal
	ADA	12	30	Normal
	PCR MTB	12	30	Normal
	VDRL	8	20	Normal
	OCB	6	15	Normal
Muscle biopsy	4	10	Atrophied muscle fibers	

**Discussion:-**

The study entitled “Clinical Profile of Motor Neuron Disease in Kashmir Valley” was a hospital based prospective study conducted in the Postgraduate Department of Medicine, SMHS Hospital, an associated hospital of Government Medical College, Srinagar during 2009 to 2011. 40 patients of MND visiting OPD / IPD of Department of Medicine, SMHS Hospital were included for the study

Out of 40 patients, 26 (65%) were males and 14 (35%) were females. Male to female ratio was 1.85:1, suggesting a male predominance. Similar gender distribution has been reported by Bracco L et al<sup>8</sup> who found male to female ratio of 1.3:1, Lopez Vega JM et al<sup>9</sup> reported male to female ratio of 1.78:1, Yoshida S et al<sup>10</sup> found male to female ratio of 1.85:06, Argyriou AA et al<sup>11</sup> reported male to female ratio of 1.44:1. Male predominance has also been reported by Govoni V et al<sup>12</sup> Swenson LW et al<sup>13</sup> and Saha et al<sup>14</sup>.

Majority of the patients in our study were falling in the age group of 51-60 years (18 out of 40, 45%) followed by 61-70 years age group (10 out of 40, 25%).

The peak age group involved in motor neuron disease has been 6<sup>th</sup> to 7<sup>th</sup> decade as reported by Yoshida S et al<sup>10</sup> at 60-69 years, Annegers JF<sup>15</sup> reported peak age group at 65-70 years, Hojer-Pederson E et al<sup>16</sup> reported peak age group at 64±10 years, Fong G et al<sup>17</sup> reported peak age group at 60-69 years. There have been a few studies reporting even a later peak age group like Mandrioli J et al<sup>18</sup> who reported 75-79 years as peak age group, Piemonte et al<sup>19</sup> reported 70-79 years age as peak age group. The peak age group in our study was a decade earlier compared to most of the literature cited, though Saha SP et al<sup>14</sup> from India has reported 41-50 years as the peak age group in his study.

Higher peak age of onset was noticed in the female compared to male. The most common presenting symptom of the patients in our study was found to be weakness of the muscles (30 patients out of 40, 75%) followed by wasting of muscles (28 patients out of 40, 70%). Saha SP et al<sup>14</sup> from India has also reported weakness and wasting of muscles as the most common presenting symptom in 80% cases.

The most common motor system finding on examination was fasciculations seen in 36 patients (90%) followed by decreased power seen in 34 patients (85%), decreased bulk and decreased tone was found in 32 patients each (80% each). Chopra et al<sup>20</sup> reported fasciculations in 80% cases while Saha SP et al<sup>14</sup> found fasciculations in 52% of cases.

The most common pattern of onset of disease was limb onset 26 patients (65) followed by bulbar onset 14 patients (35%). Among the limb onset (n=26), upper limb onset was found in 16 patients out of 26 (61.4%), lower limb onset was found in 7 patients out of 26 (26.9%). One patient each had monomelic, paraparetic and flail arm presentation. The European Subgroup Study<sup>21</sup> (Italy, Spain, Germany) has found limb onset in 82% patients and bulbar onset in

18% of patients. Onset of muscle weakness has been reported<sup>22</sup> more common in the upper than the lower extremities but in 25% of patients weakness begins in bulbar innervated muscles.

Regarding cranial nerves the most common involved cranial nerve was 12<sup>th</sup> nerve seen in 24 patients (60%) followed by 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nerves respectively involved in 8 (20%), 8 (20%) and 6 (15%) cases. In none of the patients were other nerves involved though Saha SP et al<sup>14</sup> has reported cranial nerve 12<sup>th</sup> as the most common nerve involved in 50% cases followed by 9<sup>th</sup> and 10<sup>th</sup> in 40% cases each and 11<sup>th</sup> in 16% cases.

There have been many studies relating motor neuron disease with the environmental factors like rural residence, socioeconomic status, occupation, exposure to heavy metals or toxins, prior surgical intervention, prior trauma.

Bharucha NE et al<sup>23</sup> related rural farming and lower socio-economic status with the occurrence of motor neuron disease. Granieri E et al<sup>24</sup> found higher incidence of motor neuron disease in farmers and patients of rural areas and patients with prior history of trauma. GawelM et al<sup>25</sup> has found increased incidence of motor neuron disease in patients with antecedent back injury and electric shock. Holloway SM et al<sup>26</sup> found relation between motor neuron disease and electric workers and rubber workers. Mandrioli J et al<sup>18</sup> found higher incidence in mountainous areas where agriculture was more common. But there have also been studies which have found no relation between motor neuron disease and environmental exposure. GawelM et al<sup>25</sup> found no increased incidence of head injuries, fractures or malignancy in cases of motor neuron disease compared to controls. Bharucha NE et al<sup>23</sup> found no relation of motor neuron disease with urbanization, lead or mercury exposure. TM Li et al<sup>27</sup> found no relation with occupational exposure to leather products, trauma or surgical procedures to the motor neuron diseases. Govoni V et al<sup>12</sup> found no relation as such with the rural residence.

In our study, most of the patients were labourers and farmers and belonging to the rural areas. Few patients were also exposed to prior surgery, trauma but it needs a study on a larger scale before any definite conclusion can be drawn.

Role of neuroimaging in motor neuron disease is primarily to rule out the secondary causes of motor neuron disease. Per se there are no specific findings reported for motor neuron disease, though cortical hyperintensities have been reported by many investigators. In our study majority of the cranial MRIs were normal, however, 12 patients (30%) had corticospinal region hyperintensities.

### **Conclusion:-**

A total of 40 patients of motor neuron disease were studied, out of which 26 (65%) were males and 14 (35%) were females. Male to female ratio was 1.85:1. The most common involved age group was 51-60 years (45%) which is a decade earlier than most of the studies. Peak age of onset in females was found to be a decade later than males. Bulbar onset was found in 35% of cases which is higher compared to most of the studies. Most common cranial nerve affected was 12<sup>th</sup>. Most of the patients were labourers or farmers by profession. No definite relation was found between environmental exposures with the disease.

Motor neuron disorders appear to be a clinically heterogeneous disorder with varied clinical presentation encompassing a range of upper or lower motor neuron dysfunction or both.

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