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ORIGINAL ARTICLES

Association of Motor Unit Number Estimation with Amyotrophic Lateral Sclerosis

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Abstract:

Background: *Amyotrophic lateral sclerosis (ALS) is the most common type of motor neuron disease (MND) where both upper motor neuron (UMN) and lower motor neuron (LMN) are affected. It is a neurodegenerative disease which is relentlessly progressive and presently incurable. Motor unit number estimation (MUNE) can be a valuable tool for assessing ALS. MUNE is an electrophysiological technique that estimates the number of functioning motor units in a given muscle or group of muscles. MUNE is an electrophysiological measurement which is simple and can be done in basic electrophysiology setting. It can be used as a diagnostic as well as prognostic marker of ALS so that patient can undergo an early therapeutic trial. Previous study also shows that it can differentiate ALS from other potential mimic disorders.* ***Objective:*** *The objective of this study is to see association of MUNE with ALS.* ***Methods:*** *This cross-sectional comparative study was done in the Department of Neurology, BSMMU, Dhaka, from January 2020 to September 2021. Total 44 subjects, 22 ALS patients and 22 age & sex matched control group (CG), were enrolled after satisfying the selection criteria. According to El Escorial diagnostic criteria ALS patients were sub grouped into definite, probable and possible ALS. Severity was assessed by ALS functional rating scale-revised (ALSFRS-R). Then electrophysiological study was done to measure MUNE both in ALS patients and control group by multipoint incremental stimulation based method. Collected data were analyzed by SPSS (26 version) for windows software to observe association of MUNE with ALS.* ***Results:*** *MUNE was found significantly reduced in ALS patients than control group ($MUNE_{ALS}$ -63.3 ±27.5, $MUNE_{CG}$ – 158.3±27.3; p<0.001). Possible, probable and definite ALS patients were also differentiated from control group by MUNE ($MUNE_{Definite}$ – 51.7±19.7, $MUNE_{Probable}$ – 55.8±30.5, $MUNE_{Possible}$ – 79.4±24.2 and $MUNE_{CG}$ – 158.3±27.3; p<0.001). MUNE was positively correlated (r = +0.765, p<0.001) with severity status (ALSFRS-R) and negatively correlated (r = -0.755, p<0.001) with duration of disease. Receiver operating characteristic (ROC) curve analysis showed that MUNE reliably differentiated ALS patients from control group with a cut-off value 117.75 exhibiting 99.0% sensitivity and 90.9% specificity.* ***Conclusion:*** *There was significant association of MUNE with ALS. MUNE also reliably differentiated ALS from control group with high diagnostic accuracy. MUNE had also significant association with severity status and duration of ALS.*

Key words: *Motor Unit Number Estimation, Amyotrophic lateral sclerosis.*

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Introduction:

Motor neuron disease (MND) is a progressive degenerative disease of the motor neurons of motor cortex, brainstem, and spinal cord[1]. The prevalence of MND is 4.06-7.89 per 100,000 in most parts of the world, except the Western Pacific foci[2]. The annual incidence rate of the disease varies from 0.5 to 2.6 per 100,000 population[3]. The incidence increases with age with a mean age of onset is 63 years[4]. ALS affects people worldwide with an incidence of about 1/100,000[5,6]. The risk increases after the age of 40 years and peaks in 58-63 years for sporadic disease and 47-52 years for familial disease but incidence decreases rapidly after 80 years of age. The male to female ratio is about 1.3 to 1.5 for sporadic ALS; the ratio becomes closer after 70 years and in case of familial ALS[7]. Nerve conduction study (NCS) and electromyography (EMG) have been used to diagnose ALS and are relatively accurate methods for diagnosing ALS[8,9,10]. But these methods do not reveal the severity of the disease and the rate of its progression. Therefore, a quantitative electrophysiological method is needed to monitor disease severity, rate of progression, and response to treatment. Motor unit number estimation (MUNE) can be a valuable tool for assessing ALS regarding severity and rate of progression[8,9,10]. Motor Unit Number Estimation (MUNE), first described by McComas in 1971, is suitable to evaluate the number of functioning Motor Units (MU) in a muscle[11]. Motor unit number estimation (MUNE) can be effectively correlated with functional decline in ALS. Several types of MUNE methods have been found to be useful in diagnosis and follow-up of ALS[12]. In this context, it is time demanding to establish relationship between motor unit number estimation (MUNE) and ALS.

Materials and Methods:

This cross sectional comparative study was done in the Neurology Department of BSMMU from January 2020t0 september 2021. After the approval from Institutional Review Board, 22 ALS patients and 22 Healthy control group were selected. The utility of study was explained to all study subjects and written informed consent was taken. All ALS patients were recruited after meeting Revised El Escorial diagnostic criteria as definite, probable and possible ALS with no family history of ALS. Patients' functional status or severity was evaluated by ALS Functional Rating Scale-Revised (ALSFRS-R). Age and sex matched volunteers were selected as comparison group after meeting inclusion and exclusion criteria. Data were collected through face-to-face interview using semi-structured questionnaire having selected variables according to objectives. Data were collected through face-to-face interview using semi-structured questionnaire having selected variables according to objectives. MUNE tests were performed by using NIHON KOHDEN Neuropack MEB-9400 S1 Series EMG/NCV/EP Measuring System in the department of neurology, BSMMU, Dhaka.

For the present study, the multipoint incremental method with the Shefner's modification (a combination of both multiple point stimulation and manual incremental stimulation) was selected. This method is noninvasive, threshold stimuli were well tolerated, Motor fibers of the ulnar nerve was studied. Disposable, self-adhesive recording electrodes (strips 12 -22 mm) was placed on ADM muscle innervated by the ulnar nerve of the more affected hand (recording area 4 -7 mm) after cleaning the skin surfaces and using electrolyte gels. First, the maximal CMAP was obtained in the most distal location using supramaximal stimuli. SMUP was acquired by averaging several potentials with an increased amplitude, using the "all or none" method with stimulation of an increasing intensity. The acceptable amplitude of the initial response was not less than 25 μV. The amplitude of 10 SMUP responses at the three locations was summed and divided by 10 to obtain the mean amplitude of an average surface-detected SMUP. MUNE is equal to the maximal CMAP amplitude divided by the average SMUP amplitude.

Result:

Among 44 study subjects, 22 ALS patients along with 22 age and sex matched healthy control group were selected. The mean age of ALS patients was 40.41±12.5 years with age range 22-70 years and mean age of control group was 38.40±10.87. majority of study subjects were above 30 years of age.

Table-I

Distribution of study subjects by age (n=44)

Age (years)	ALS patients (n=22) No.(%)	1Control group (n=22) No.(%)	p-value
< 30	6(27.3)	6(27.3)	
31-50	11(50.0)	13(59.1)	
>50	5(22.7)	3(13.6)	
Total	22(100)	22(100)	
Mean±SD	40.41±12.5	38.40±10.87	0.574^{ns}
Range	22-70	20-54	

Data were expressed as frequency, percentage within parenthesis and mean ± SD
Unpaired t-test was done to analyze the data, ns = not significant
ALS: Amyotrophic lateral sclerosis

Majority of ALS patients were presented with Limb onset ALS followed by bulbar onset.

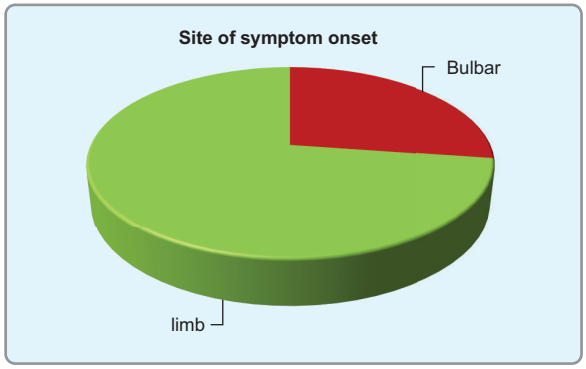


Fig.-1: *Pie diagram showing site of symptom onset of ALS*

Among ALS patients, majority were in moderate state of severity. Only 22.7% patients were in severe state.

Table-II

Distribution of the ALS patients by severity (ALSFRS-R) (n=22)

ALS patients by severity	Frequency	Percentage
Mild (>40)	8	36.4
Moderate (30-39)	9	40.9
Severe (20-29)	5	22.7
Advanced (<20)		
Total	22	100.0

Data were expressed as frequency and percentage
ALS: Amyotrophic lateral sclerosis
ALSFRS-R: ALS functional rating scale - revised

Comparison of MUNE among ALS and control group

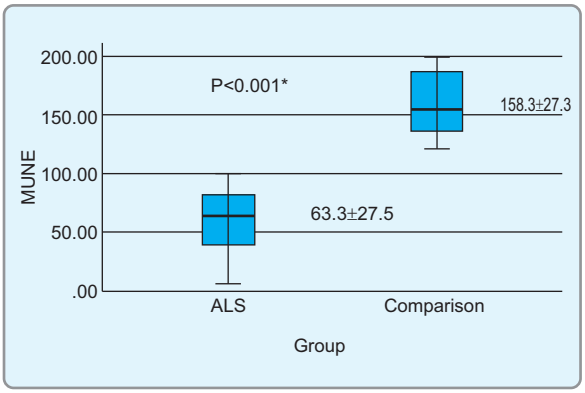
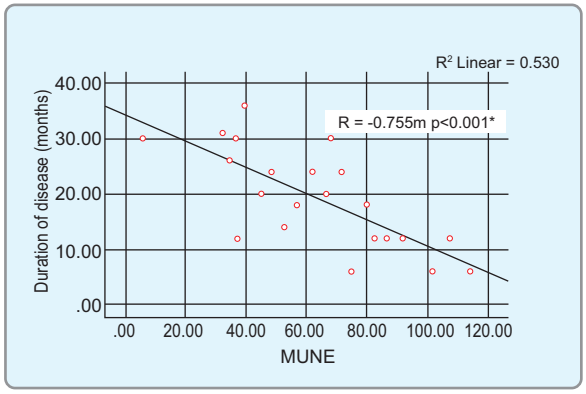
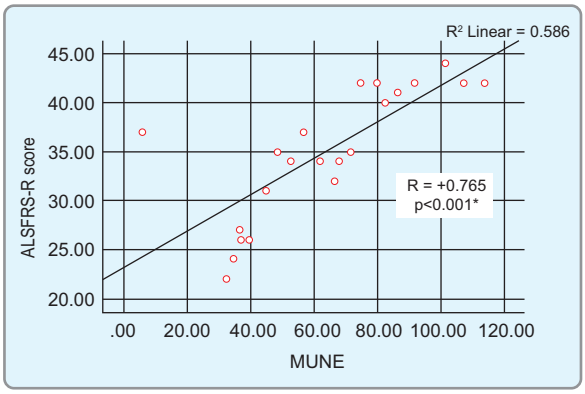


Fig.-2: *Box-whisker plot showing MUNE of ALS and Control group*



Pearson's correlation coefficient test

Fig.-3: *Scatter diagram showing the correlation of MUNE with duration of disease(months).*



Pearson's correlation coefficient test

Fig.-4: *Scatter diagram showing the correlation of MUNE with severity of ALS(ALSFRS-R)*

Discussion:

This study was intended to see the association of Motor Unit Number Estimation (MUNE) with amyotrophic lateral sclerosis and to assess its diagnostic utility in ALS so that role of MUNE can be established as a reliable neurophysiological tool for diagnosis of disease and also assess the severity and progression of ALS patients.

In this study 22 ALS patients and 22 age & sex matched comparison group were recruited after meeting selection criteria by convenient purposive sampling. The mean age of ALS patients was 40.41 ± 12.5 years with age range 22-70 years and mean age of control group was 38.40 ± 10.87 years with age range 20-54 years. In present study mean age of ALS was found to be low in comparison to other studies performed in different population group[13,14,15,16]. But previous study in India by Nalini et al 2008 showed that mean age of ALS(n=1153) was 46.2±14.1 that was consistent with present study and also previous study by Escorcio-Bezerra 2016 showed mean age was 42.3±16.4(range: 24-75)[17].

Regarding sites of symptom onset in ALS patients, majority had limb onset ALS (72.7%) and bulbar onset ALS was in 27.3% patients. Several previous studies showed consistency with these findings[18].

Severity state of disease was assessed by ALS functional rating scale – revised (ALSFRS-R) where there were 8 functional domains with 6 points in each. Total score was 48. Based on ALSFRS-R severity of ALS was categorized as mild (>40), moderate (30-39), severe (20-29) and advanced (<20). In present study 40.9% of ALS patients were in moderate, 36.4% in mild, 22.7% in severe state at the time of assessment which was consistent with a previous study where median ALSFRS-R score was in moderate state of severity[19]. There was no significant difference of severity state between definite and probable type of ALS (mean ALFRS-R score - 31.0±6.9 vs. 35.0±6.6). But 62.5% possible ALS patients were in mild state of severity (mean ALFRS-R score – 37.9.0±5.8).

MUNE was significantly reduced in ALS patients than control group ($MUNE_{ALS}$ – 63.3 ± 27.5, $MUNE_{CG}$ -158.3±27.3; (P < 0.0001) in this study. This finding was consistent with previous study - $MUNE_{ALS}$ - 88.1 ± 56.1, $MUNE_{CG}$ – 150.6 ± 40.7; p<0.0001[14] and (ALS- 41.7 ± 32.1 vs. CG-87.7 ± 14.5)[10]. These were all CMAP based study. Previously Ibrahem et al. (2021) showed MUNE to be significantly correlated with severity (according to ALSFRS-R score) of disease (r = +0.398, p<0.04)[20]. In present study also MUNE was found to be positively correlated (r = +0.765, p<0.001) with severity of disease in ALS patients indicating the fact that along with decline of functional status of ALS patient's values of MUNE reduced significantly. Another study Liu et al. 2009 also observed that MUNE correlated significantly with ALS-FRS ($P < 0.05$)[19].

In this study we also found that MUNE had significant negative correlation (r = -0.755, p<0.001) with duration of disease in ALS patients reflecting the fact – along with the increase in duration of disease values of MUNE reduced significantly that also consistent with previous study by Ibrahem et al. 2021(r= -0.540, p<0.003)[20].

In present study ROC revealed that MUNE reliably differentiated ALS from comparison group with a cut off value 117.75, AUC - 0.989, p<0.0001, Sensitivity - 99.0% and Specificity – 90.9%. These findings were consistent with previous study by Ibrahem et al. (2021) (with a cut off value-180.5, AUC -0.965, p<0.0001, 81% Sensitivity and 95% Specificity)[20].

Conclusion:

In present study showed significant association of Motor unit number estimation (MUNE) with amyotrophic lateral sclerosis (ALS). MUNE was significantly reduced in ALS patients than control group (CG). . MUNE also had significant negative correlation with duration of disease and positive correlation with severity state (ALSFRS-R) in ALS. ROC curve analysis also revealed that MUNE (117.75) reliably differentiated ALS from CG with high sensitivity (99.0%) and specificity (90.9%).

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