CMAP Amplitude of Median Nerve - A Prognostic Marker of Amyotrophic Lateral Sclerosis

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KEYWORDS

Amyotrophic lateral sclerosis (ALS), Functional rating scale revised ALSFRS-R, Compound muscle action potential (CMAP)

ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is an incurable relentlessly progressive neurodegenerative disease. A nerve conduction study and electromyogram are routinely used for diagnosis, and the compound muscle action potential (CMAP) amplitude of the median nerve in nerve conduction study is a key prognostic marker at the time of diagnosis enabling carly therapeutic trial. Previous studies have shown that a decreased median nerve amplitude strongly correlates with the functional status of ALS, making it a useful quantitative prognostic marker.

Objectives of the study: The study aims to determine the association of CMAP amplitude of median nerve with prognosis of ALS.

Materials and Methods: The research was conducted at the Department of Neurology, BSMMU, Dhaka, from April 2023 to September 2024, and it involved 38 subjects. Among them, 19 ALS patients had normal CMAP amplitude of median nerve, while 19 ALS patients had decreased CMAP amplitude of median nerve and met the selection criteria. Patients with ALS were diagnosed based on the Revised El Escorial diagnostic criteria, and Severity of their condition was assessed using the ALS functional rating scale-revised (ALSFRS-R). Data were analyzed using SPSS (26 versions) for Windows to observe the association between CMAP amplitude of the median nerve with the functional status of ALS.

Result: ALSFRS-R was significantly reduced at 6 months than at the time of diagnosis in ALS patients with decrease CMAP amplitude of median nerve than normal CMAP amplitude. Multivariate analysis revealed ALSFRS-R at diagnosis and decrease CMAP amplitude of median nerve were significantly associated with poor outcomes. Survival model analysis revealed ALS patients with decrease CMAP amplitude of median nerve had shorter survival time than with ALS with normal CMAP amplitude patients.

Conclusion: Patients with decrease CMAP amplitude of median nerve may experience shorter survival times and poorer functional outcomes. This can serve as a valuable prognostic marker for patients with ALS.

INTRODUCTION

Motor neuron disease (MND) is a progressive degenerative disease of the motor neurons of motor cortes, brainstem, and spinal cord [1]. The prevalence of MND is 4-6 per 100,000 in most parts of the world, except the Western Pacific foci [2]. ALS is a relentlessly progressive. presently incurable disorder with an incidence of about 1/100,000 [3]. ALS is a progressive disease, 50% patients die within 30 months of symptom onset and 20% of patients survive between 5 years and 10 years of symptoms. As many as 10% of patients with ALS survive for more than 10 years.

According to the Revised El Escorial Criteria and Awaji Consensus recommendations, signs of involvement of both upper (UMN) and lower motor neurons (LMN) are required the diagnosis of ALS. The disorder should be progressive, and other mimicking disorders must be ruled out by electrophysiological, imaging, and other laboratory tests [5]. Routine EMG and nerve conduction studies are still incorporated into the diagnostic criteria for amyotrophic lateral sclerosis (ALS) (El Escorial). However, these techniques have not been proven to be effective in monitoring disease progression or assessing treatment effects. Nerve conduction study (NCS) and electromyography (EMG) have been used to diagnose ALS and are relatively accurate methods for diagnosing ALS [6]. But these methods do not reveal the severity of the disease and the rate of its progression. Findings of motor nerve conduction study in patient with ALS typically showed slight abnormalities, including amplitude of CMAP.

The amplitude of compound muscle action potential (CMAP) is widely used in clinical practice as an important electrophysiological index to detect motor axonal damage. It was found that the decrease in the CMAP amplitude of the motor nerve in the early stage was significantly related to motor axonal hyperexcitability. It was found the relationship between motor axonal dysfunction in the early stage and in disease progression in some studies in patients with ALS [7]. After all, CMAP amplitude decreased as the severity of muscle weakness increased. Some bed side clinical methods used to monitor disease progression such ALSFRS-R score. But those are qualitative methods and cannot predict accurately the functional outcome of ALS. An early anticipation of the clinical course is important to plan the best support for both the patient and his family.

Therefore, a quantitative electrophysiological method is needed to predict the functional outcome of ALS. Measurment of CMAP amplitude can be a valuable tool for assessing ALS regarding this issue [6].

Previous study showed that Decrease CMAP amplitude of median nerve have impact on prognosis of ALS patient and there's some pattern of changes in NCS in ALS patients. But the clinical significance of CMAP amplitude found in patients with ALS has not fully elucidated. The motor nerve conduction of the median in the upper extremities was examined bilaterally by routine methods. The amplitude of the CMAP was recorded. The purpose of this study is to evaluate the association of CMAP amplitude with the functional outcome of ALS with a view to early prediction of prognosis of the disease.

METHODOLOGY

Study Settings and Population

This was designed as a prospective Comparative study. This present study was carried out from May 2023 to September 2024. The study was conducted in the neurophysiology clinic, Inpatient and Outpatient Department of Neurology (BSMMU), Super Specialized Hospital, Bangabandhu Sheikh Mujib Medical University. In this study, 38 ALS patients were included after meeting the selection criteria by purposive non-random sampling.

Study Procedure

After getting clearance from the departmental Technical Committee and the Institutional Review Board (IRB), the study was conducted. The sample was recruited from the Neuromuscular Disorder Clinic, inpatient and outpatient neurology department, BSMMU, Dhaka, after matching inclusion and exclusion criteria. The utility of the study was explained to all study subjects, and written informed consent was taken. Data were collected through face-to-face interviews using a semi-structured questionnaire having selected variables according to objectives. Demographic profile, Clinical history, physical Examination findings, electrophysiological findings, related laboratory reports, and other related information of each subject were recorded in a data sheet. All ALS patients will be recruited after meeting Revised El Escorial diagnostic criteria as definite, probable, probable lab-supported, and possible ALS with no family history of ALS. Patients' functional status was evaluated by the ALS Functional Rating Scale-Revised (ALSFRS-R) at the time of diagnosis and 6 months. CMAP amplitude of four

nerves (median, ulnar, tibial, peroneal) was measured in ALS patients by using NIHON KOHDEN Neuropack MEB-9400 S1 Series EMG/NCV/EP measuring system in the department of Neurology, BSMMU, Dhaka. All ALS patients were divided into two groups by means of CMAP amplitude. Subjects' right to withdraw from the study at any point was ensured. Information obtained from study subjects was kept confidential except for research purposes only.

Data processing and analysis

Statistical analysis was carried out using SPSS 26.0 for Windows software. Continuous variables were presented as mean standard deviation, while categorical variables were expressed as percentages. Group comparisons for continuous variables were conducted using Unpaired t-tests. The association of variables with functional outcomes was tested using Chi Square tests with a significance level set at $p < 0.05$ to determine statistical significance.

Ethical consideration

The protocol of this study involving human subjects was submitted to the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU) for approval. A certificate of ethical clearance was obtained after proper review by the members of the IRB. The aims and objectives of the study, along with its procedures, risks, and benefits, were explained to the respondents in the easily understandable local language and informed written consent was obtained from each. It was assured that all information and records were kept confidential.

RESULTS

This longitudinal study from April 2023 to September 2024, was carried out in the neuromuscular problem clinic in the inpatient and outpatient neurology department at BSMMU, Dhaka. 38 ALS patients who satisfied the selection criteria were included in this study by selective non-random sampling. Data were gathered by conducting in-person interviews with study participants using a particular questionnaire in order to determine whether normal and longer distal motor delay are associated with better functional outcomes in individuals with amyotrophic lateral sclerosis. After analysis using SPSS (version 26) for Windows software, the acquired data will be presented in this chapter in the form of figures and tables.

Table-1: Age distribution of the study subjects ALS patient (N=38)

Age group (year)	Decreased CMAP Amplitude of median nerve		Normal CMAP Amplitude of median nerve		*p*-value
		(n=19)	(n=19)		
	n	(%)	n	(%)	
<30	3	15.8%	2	10.5%	0.429
31-50	8	42.1%	12	63.2%	
>50	8	42.1%	5	26.3%	
Total	19	0.0%	19	100.0%	
Mean ± SD	48.6 ± 14.3		45.5 ± 11.1		0.460
Range (min-max)	(18-70)		(18-70)		

p-value obtained by Unpaired t-test, $p<0.05$ was considered as a level of significant

There were no discernible age differences between the lowered amplitude of median nerve and normal amplitude groups based on the age distribution of the study participants. To be more precise, there was no significant difference in the frequencies of participants in each age category between the two groups ($p = 0.429$ for <30 years old, $p = 0.460$ for mean age). The findings imply that, in this study population, age is not a major predictor of amplitude decline.

Table 2: Distribution of study subjects ALS patients by presenting complaints (N=38)

Presenting complaints	Decreased CMAP Amplitude of median nerve (n=19)		Normal CMAP Amplitude of median nerve (n=19)		*p*-value
	n	(%)	n	(%)	
Onset of symptoms					
Limb	14	73.7%	13	68.4%	0.721
Bulbar	5	26.3%	6	31.6%	0.721
Presenting complaints					
Weakness in all 4 limbs	9	47.4%	14	73.7%	0.097
Both upper limb	11	57.9%	15	78.9%	0.163
Tongue atrophy	10	52.6%	5	26.3%	0.097
Small muscle atrophy	17	89.5%	17	89.5%	1.000
Walking difficulty	9	47.4%	14	73.7%	0.097
Muscle twitching	15	78.9%	18	94.7%	0.15
Speech difficulty	9	47.4%	6	31.6%	0.319
Swallowing difficulty	8	42.1%	3	15.8%	0.074
Nasal regurgitation	6	31.6%	3	15.8%	0.252

p-value obtained by Chi-square test, $p<0.05$ was considered as a level of significant

38 research participants were divided into two groups based on the presenting complaints they had: those with reduced amplitude (n = 19) and those with normal amplitude (n = 19), as shown in the table. The p-values for each complaint that is presented are also shown in the chi-square test findings.
There are no discernible correlations between decreased amplitude and the remaining presented complaints ($p > 0.05$). The absence of statistically significant correlations implies that there may not be a substantial correlation between the amplitude of muscle contraction and the presenting complaints.
The results of this study indicate that, to fully understand the underlying mechanics and therapeutic implications of these discoveries, more investigation is required.

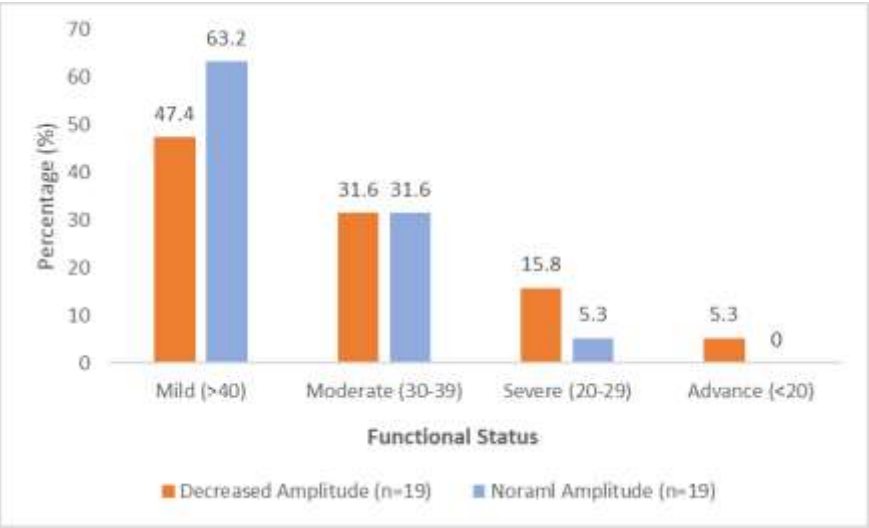

Figure 1: Bar diagram showing the comparison of functional status of normal and decreased CMAP at diagnosis (n=38)

Table 3: Distribution of ALS patients by means of functional states at 6 months (N=38)

ALS patients by severity and death at 6 months	Decreased Amplitude (n=19)		Normal Amplitude (n=19)		*p*-value
	n	(%)	n	(%)	
Mild (>40)	3	15.8%	8	42.1%	0.021
Moderate (30-39)	4	21.1%	9	47.4%	
Severe (20-29)	5	26.3%	1	5.3%	
Advance (<20)	2	10.5%	0	0.0%	
Death	5	26.3%	1	5.3%	
Total	19	100.0%	19	100.0%	

p-value obtained by Chi-square test, $p<0.05$ was considered as a level of significant

The data indicates that the probability of death for patients with ALS is significantly correlated with the severity of functional status six months after diagnosis (p-value = 0.021, *significant). More specifically, compared to patients with decreased amplitude (15.8%), those with normal amplitude (42.1%) were more likely to be classified as mild (>40). On the other hand, patients who had an advanced (<20) or severe (20-29) functional status were more likely to have reduced amplitude. The findings imply that, in comparison to patients with more severe functional status, individuals with milder functional status have a higher chance of surviving six months after diagnosis.

DISCUSSION

The purpose of this study was to evaluate the predictive value of this difference between normal and decrease amplitude of median nerve with the functional outcome of ALS patients. Furthermore, decrease amplitude can be established as a simple and reliable quantitative prognostic indicator for predicting functional outcomes at an earlier stage of ALS diagnosis. According to the study, ALS patients who had decreased amplitude of median nerve had a much lower survival rate and poor outcome than those who had normal amplitude. In this study 38 ALS patients were recruited 19 with normal amplitude and 19 with decrense amplitude.

The mean age of ALS patients with normal amplitude was 45.5 ± 11.1 years and the mean age of ALS patients with decrease amplitude was 48.6 ± 14.3 years. The age distribution of the study subjects with ALS (n=38) did not reveal any significant differences between the groups with decreased CMAP amplitude of the median nerve and those with normal amplitude. Specifically, the frequency of participants in each age category (<30 years, 31-50 years, and >50 years) did not differ significantly between the two groups ($p = 0.429$ for 30 years old, $p = 0.460$ for mean age). This suggests that age is not a significant predictor of amplitude decline in this study population. These findings are consistent with previous research that has found no significant correlation between age and CMAP amplitude decline in ALS patients [8].

The most frequent presenting complaints in our research participants were small muscle atrophy of the hand, muscular twitching, and weakness in all four limbs. And those with bulbar involvement also reported difficulties swallowing and speaking, nasal regurgitation, and tongue wasting.

Regarding sites of symptom onset in ALS patients, most had limb onset ALS in 14 (73.7%) and 13 (68.4%) in normal amplitude group whereas bulbar onset ALS in 5 (26.3%) patients in decrease amplitude group and 6 (31.6%) in normal amplitude group. Several previous studies consistently supported these findings [12,13,14].

This study presents the distribution of 38 ALS patients by their functional status at diagnosis, categorized into four severity levels based on amplitude: mild (>40), moderate (30-39), severe (20-29), and advance (<20). The results show that 47.4% of patients with decreasing amplitude and 63.2% of patients with normal amplitude were classified as mild (>40). The Chi-square test was used to assess the significance of the relationship between amplitude and severity, yielding a p-value of 0.488, which indicates that the observed differences are not statistically significant. This finding suggests that there is no significant correlation between the amplitude of ALS

patients and their functional level at diagnosis. In other words, the amplitude of ALS patients does not significantly affect their functional status at diagnosis. This is consistent with previous studies that have found no significant correlation between muscle strength and functional impairment in ALS patients [8,10].
The lack of significant correlation between amplitude and severity may be due to the fact that ALS is a complex and heterogeneous disease, characterized by varying degrees of motor neuron degeneration and axonal damage. Additionally, the severity of ALS may be influenced by factors beyond muscle strength, such as cortical involvement, respiratory function, and nutritional status [11]. The results of this study suggest that there is no significant correlation between the amplitude of ALS patients and their functional level at diagnosis. This finding highlights the need for a comprehensive assessment of ALS patients, including evaluation of multiple clinical features and domains, to better understand their functional status and prognosis.

This study suggests that the distribution of ALS patients by their functional status at 6 months after diagnosis, with a significant correlation found between the severity of functional status and the probability of death (p-value = 0.021, *significant).

The study's results also highlight the importance of monitoring functional status in ALS patients, as it can provide valuable information about their prognosis and overall survival. Early identification of patients with more severe functional impairment may enable healthcare providers to initiate aggressive interventions and provide targeted care to improve their quality of life and prolong their survival.

However this study presents a significant correlation between the severity of functional status and the probability of death in ALS patients at 6 months after diagnosis. The findings suggest that milder functional status is associated with a higher chance of survival, emphasizing the importance of monitoring functional status in ALS patients.

This study presents a comparison of the mean Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALS-FRS-R) scores between two groups of patients with amyotrophic lateral sclerosis (ALS): those with decreased amplitude and those with normal amplitude. The findings suggest that at the time of diagnosis, there was no significant difference in the mean ALS-FRS-R score between the two groups ($p = 0.176$) The mean scores were 36.8 ± 7.92 for patients with decreased amplitude and 39.9 ± 5.7 for patients with normal amplitude [8].

However, at six months, a statistically significant difference was observed in the mean ALS-FRS-R score between the two groups ($p = 0.011$) The mean score for patients with normal amplitude remained relatively consistent at 37.7 plus/minus 4.9 whereas the mean score for patients with decreased amplitude decreased significantly to 31.3 plus/minus 4.8 These findings suggest that
patients with ALS and decreased amplitude may experience a more rapid decline in Runctional ability over time compared to those with nonnal amplitude. This is consistent with previous studies that have shown that patients with reduced muscle strength and amplitude are more likely to experience a faster decline in functional ability [9].

This study highlights the importance of monitoring patients with ALS over time to better understand the natural history of the disease and to identify potential predictors of disease progression.

CONCLUSION

In conclusion, a significant association was found between decrease amplitude and the functional outcomes of ALS patients. However, ALS patients with decrease amplitude had poorer prognoses and significantly reduced survival times than those with normal amplitude. In addition, NCS is simple to perform and routinely measured tests for the differential diagnosis of ALS. Therefore, CMAP amplitude could be strong prognostic marker in patients with ALS.

Ethical Issue: All patients gave informed written consent and the study was approved by Institutional Review Board of Bangabandhu Sheikh Mujib Medical University.

Conflict of Interest: None

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