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Electrodiagnostic profile of conduction slowing in amyotrophic lateral sclerosis

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ABSTRACT

Objective: Since motor nerve conduction slowing can occur due to loss of large axons, we investigate the conduction slowing profile in amyotrophic lateral sclerosis (ALS) and identify the limits beyond which the diagnosis of exclusive axonal loss is unlikely.
Methods: First, using linear regression analysis, we established the range of motor conduction slowing in 76 chronic inflammatory demyelinating polyneuropathy (CIDP) patients. Demyelinating range confidence intervals were defined by assessing conduction velocity (CV), distal latency (DML), and F-wave latency (F) in relation to distal compound muscle action potential (CMAP) amplitude of median, ulnar, fibular, and tibial nerves. Results were subsequently validated in 38 additional CIDP patients. Then, the newly established demyelination confidence intervals were used to investigate the profile of conduction slowing in 95 ALS patients.
Results: CV slowing, prolonged DML, and abnormal F were observed in 22.2%, 19.6%, and 47.1% of the studied nerves respectively in ALS patients. When slowing occurred, it affected more than one segment of the motor nerve, suggesting that CMAP amplitude dependent conduction slowing caused by an exclusive loss of large axons is the main mechanism of slowing. No ALS patient had more than 2 nerves with CV slowing in the confidence interval defined by the regression equations or the American Academy of Neurology (AAN) research criteria for CIDP diagnosis.
Conclusions: The presence of more than two motor nerves with CV slowing in the demyelinating range defined by the regression analysis or AAN criteria in ALS patients suggests the contribution of acquired demyelination or other additional mechanisms exist in the electrodiagnostic profile of ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare progressive and ultimately fatal neurodegenerative disorder characterized by selective degeneration of upper motor neurons (MNs) in the cerebral cortex and lower MNs of the brain stem and spinal cord, for which there is currently neither a cure nor a truly effective treatment [1,2]. Electrodiagnostic testing plays a key role in confirming the diagnosis of ALS and excluding other axonal or demyelinating polyneuropathies. However, abnormal motor nerve conduction slowing has been

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reported in ALS and has been attributed to the loss of large axons and distal axonopathy [3–7], which complicates the differentiation of ALS from motor neuropathies [8–11]. Due to the poor prognosis of ALS, it is crucial to identify whether there are other alternative or superimposed motor neuropathies that may fit patients' nerve conduction profiles to better differentiate ALS from other motor neuropathies.

Nerve conduction studies are crucial for confirming the diagnosis of ALS and excluding mimicking disorders [3–7]. The electrodiagnostic distinction between ALS and demyelinating motor neuropathies is sometimes challenging, particularly in motor neuropathies including multifocal motor neuropathy, hereditary motor neuropathy and familial amyloid polyneuropathy [8–14]. Conduction velocity (CV) slowing may occur in ALS, especially when the compound muscle action potential (CMAP) is reduced. This slowing is usually described as a CMAP amplitude dependent conduction slowing and is attributed to the loss of large, fast conducting motor neurons. Moreover, we noticed that in the presence of a low CMAP amplitude, the correspondingly abnormal CVs, distal latencies (DML), and F-wave latencies (F) may create a complex picture including features of axonal loss and demyelination that do not fulfill the American Academy of Neurology (AAN) research criteria for chronic inflammatory demyelinating polyneuropathy (CIDP).

The objective of this study was to characterize and differentiate motor nerve conduction slowing in ALS from other neuropathies. Using a well-defined population of CIDP patients, we sought to determine the range of conduction values in ALS and develop regression equations, and confidence limits for motor nerve conduction slowing. We subsequently studied a group of well-defined ALS patients by Escorial criteria to look for overlap of motor DML, CV, and F with the CIDP group, to further characterize the distribution of conduction slowing in ALS and to determine the limits of conduction slowing beyond which the diagnosis of ALS is uncertain.

2. Materials and methods

2.1. Subjects

The protocol of this retrospective study was reviewed and approved by the Institutional Ethical Committee of New Jersey Medical School, Rutgers University (Pro0120050196). Requirement for individual patient consent was waived because the project did not impact clinical care and all protected health information was deidentified.

We retrospectively identified a group of 76 patients with CIDP using AAN research criteria for CIDP diagnosis [15]. Electrodiagnostic data from the CIDP patients was used to develop regression equations that determine, for each CMAP amplitude, the range of slowing expected from a primary demyelinating polyneuropathy. A second independent group of 38 CIDP patients, fulfilling the AAN research criteria for CIDP, was used to validate 12 equations [15]. The Wilcoxon rank sum test was used to test the hypothesis that there is no difference in the distributions of the first group of 76 patients and the second group of 38 patients with CIDP in each of the 12 equations of confidence intervals to confirm the validity of confidence intervals (all 12 p-values$>$0.05 significance level).

Electrodiagnostic data were also obtained from 95 patients diagnosed with ALS based on the Escorial revised criteria of the World Federation of Neurology [16]. Electrodiagnostic testing was performed in a quiet room with a limb temperature at or above 32 °C and using standard methods [17]. Nerve conduction study parameters including CMAP, DML, CV, and F of the median, ulnar, tibial, and fibular nerves were recorded. In the motor nerve conduction studies, stimulation was performed by a bar electrode and the recording was performed by disc electrodes. In the sensory nerve conduction studies, stimulation was performed by ring electrodes and recording was performed orthodromically by bare electrodes in both upper extremities. In lower extremities, stimulation and recording of sensory nerves was performed with bare electrodes. The study was performed orthodromically in the sural nerve and antidromically in the superficial peroneal nerve. Skin temperature was recorded using a surface probe and maintained above 32 °C. Table 1 summarizes the stimulation and recording sites for the studied nerves.

2.2. Statistical analysis

2.2.1. Regression equations

For the first CIDP group (76 patients), median, ulnar, tibial, and fibular nerve data were converted to a percentage of upper limit of

Table 1
Nerve stimulation and recording sites.

Nerves	Stimulation Sites	Recording Site
Median (motor)	Wrist, elbow	Abductor pollicis brevis
Median (sensory)	Index finger	Wrist
Ulnar (motor)	Wrist, elbow, above elbow	Abductor digiti minimi
Ulnar (sensory)	Little finger	Wrist
Radial (motor)	Mid forearm, above the elbow, axilla	Extensor indicis
Radial (sensory)	Ridge of the radius	Thumb
Median palmar (sensory)	Median Palmar	Wrist
Ulnar palmar (sensory)	Ulnar palmar	Wrist
Peroneal (motor)	Ankle, fibula head, above knee	Extensor digitorum brevis
Superficial peroneal nerve	Anterior edge of the fibula	Medial to lateral malleolus
Tibial (motor)	Ankle, knee	Flexor hallucis brevis
Sural (sensory)	Lateral malleolus	Calf
Medial Plantar (motor)	Above the ankle	Flexor hallucis brevis

normal for the DML and F responses, and lower limit of normal for the CMAP amplitude and CV. These data were then transformed to achieve a more linear relationship between CMAP amplitude and CV, DML, and F by using a square root transformation, fourth root transformation, or Log_{10} transformation. We then plotted the transformed data with CMAP in the x–axis, and the DML, CV, or F in y-axis. Using linear regression analyses, we developed equations that assessed the range of slowing in CIDP with confidence intervals that link CV, DML, and F to distal CMAP amplitude of median, ulnar, fibular, and tibial nerves. These developed equations were then used to study conduction slowing in 95 patients with ALS.

2.2.2. Data summary and statistics

Basic data summary statistics were performed using Microsoft Excel® 2016. SAS® Software (version 9.4) was used to perform advanced statistical analyses. Categorical variables were summarized by their counts and percentages, and the distribution of groups was compared using chi-square test and Fisher's exact tests. Z-test of proportions was used to compare two proportions. Continuous variables were summarized by their means and standard deviations along with ranges, and the distribution of groups was tested using *t*-test and analysis of variance. All tests for statistical significance were two-sided with a significance level of 0.05.

Linear regression was used to identify the dependence of DML, CV, and F on CMAP amplitude. Transformed CMAP amplitude was used as an independent variable and the transformed DML, CV, and F were used as dependent variables. We evaluated the slope of the regression lines, which is a measure of the relationship between the CMAP amplitude and DML, CV, and F. Pearson's coefficient (r) was used to evaluate the correlation between CMAP amplitude and CV, DML, and F. The $p < 0.05$ was considered significant and Pearson r values of >0.7 were considered as representing high correlation and those between 0.35 and 0.7 as moderate correlation.

3. Results

The regression equations were acquired by using CMAP amplitude equal to the lower normal limit and at 50% of the lower of limit normal. The range of conduction slowing in the demyelinating range is shown in Table 2.

The validity of the confidence intervals derived from the regression equations was confirmed by the demonstration that all the 12-equation data of the additional group of 38 CIDP patients were within the confidence intervals determined by the first group of 76 CIDP patients (all 12 p-values were >0.05).

Subsequently, electrodiagnostic studies of 95 patients diagnosed with ALS were analyzed. The mean age of patients in the ALS group was 58.5 ± 11.70 years. There were 58 men and 37 women. A total of 545 motor nerves were studied, including 133 median nerves, 139 ulnar nerves, 141 tibial nerves, and 132 fibular nerves. The raw data were converted to mean and range of percentage of normal for each nerve, which was summarized in Table 3. The mean CMAP amplitude of the median and ulnar nerve was relatively lower to the lower limits of normal compared to the tibial and peroneal nerve which may suggest more lower motor neuron loss in upper extremities compared to lower extremities in the studied patients.

Table 4 shows the results of the conduction slowing study in ALS patients. The results indicate that about 44.8% and 22.2% of the studied nerves had CMAP amplitudes and CV below the lower limit of normal, respectively. Only 1.4% of the studied nerves had CV slowing in the AAN demyelinating range, whereas 9.4% had CV in the equation's confidence intervals ranges ($p < 0.0001$). The most common altered motor nerve conduction velocity was observed in the ulnar nerve, followed by the tibial nerve, fibular and the median nerves (Table 3). However, the median nerve has the highest incidence of conduction slowing in the AAN demyelinating range (3.8%).

There is no significant difference in the incidence of prolonged DML between all studied nerves, although the fibular nerve has the lowest incidence of prolonged DML in the AAN demyelination range.

Prolonged DML was observed in 19.6% of the studied nerves. Only 3.3% of the studied nerves had prolonged DML in the AAN demyelinating range, whereas 11.7% had prolonged DML in the equations' confidence intervals ranges ($p < 0.0001$). Of the studied nerves, 47.1% had abnormal F (prolonged F or absent) in the ALS group. Only 15.8% of the studied nerves had abnormal F in the AAN demyelinating range whereas 31.3% had abnormal F in the equations' demyelinating confidence intervals ranges ($p < 0.0001$). The

Table 2
Conduction slowing using the regression equations and AAN criteria.

	Min DL by regression equation (ms)	Min DL by AAN criterion (ms)	Max CV by regression equation (m/s)	Max CV by AAN criterion (m/s)	Min F by regression equation (ms)	Min F by AAN criterion (ms)
CMAP 100%; F for height 65″						
Median nerve	4.7	5.6	41.9	39.2	33.8	34.8
Ulnar nerve	3.7	5.0	48.8	37.6	33.2	36.2
Tibial nerve	7.3	8.8	34.3	29.6	62.2	68.4
fibular nerve	6.7	8.1	37.2	31.2	59.8	68.4
CMAP 50%; F for height 65"						
Median nerve	5.4	6.8	39.0	34.3	35.9	43.5
Ulnar nerve	4.3	6.0	41.7	32.9	37.7	45.3
Tibial nerve	7.3	10.5	33.2	25.9	63.4	85.5
fibular nerve	6.8	9.8	36.6	27.3	60.2	85.5

AAN, American Academy of Neurology; CV, conduction velocity; DL, distal latency; F, F-wave latency; CMAP, compound muscle action potential.
Min DL: minimum distal latency value per the regression equation which is considered in the demyelinating range.
Min DL by AAN criterion: minimum distal latency value which is considered in the demyelinating range by AAN criteria.
Max CV by AAN criteria: Upper limit of conduction velocity which the conduction velocity is considered in the demyelinating range.

Table 3
Electrodiagnostic profile of ALS patients.

	Number of Nerves Studied	Laboratory Normal Nerve Conduction Values	ALS Mean	ALS Range	Converted Mean** (%)	Converted Range (%)
			Distal Latency (ms)			
Median Nerve	133	<4.5 ms	4.4 ± 1.07	2.4–8.7	97.9 ± 23.82	53.3–193.3
Ulnar Nerve	139	<4.0 ms	3.5 ± 1.11	2.2–9.8	87.2 ± 27.70	55.0–245.0
Tibial Nerve	141	<7.0 ms	5.7 ± 1.82	3.1–11.4	80.9 ± 26.04	44.3–162.9
Fibular Nerve	132	<6.5 ms	5.2 ± 1.29	1.3–10.5	79.9 ± 19.86	20.0–160.8
			Conduction Velocity (m/s)			
Median Nerve	131	<49 m/s	50.2 ± 8.15	27.0–95.2	102.4 ± 16.63	55.1–194.3
Ulnar Nerve	135	<47 m/s	53.1 ± 9.02	16.0–114.3	113.7 ± 17.95	58.5–243.2
Tibial Nerve	109	<37 m/s	41.6 ± 5.84	30.8–56.7	112.5 ± 15.77	83.2–153.2
fibular Nerve	124	<39 m/s	43.0 ± 5.65	24.0–54.0	110.3 ± 14.49	61.5–138.5
			F-wave latency * (ms)			
Median Nerve	87	*	32.0 ± 9.47	22.2–99.1	107.7 ± 30.02	75.4–317.7
Ulnar Nerve	92	*	30.5 ± 3.51	20.5–39.2	97.1 ± 10.21	65.8–118.8
Tibial Nerve	99	*	55.5 ± 6.54	43.3–70.2	94.1 ± 10.24	70.9–118.1
Fibular Nerve	86	*	52.1 ± 6.92	38.6–64.5	88.3 ± 11.31	65.2–107.1
			CMAP amplitude (mV)			
Median Nerve	132	>4.5 mV	4.0 ± 3.28	0.2–13.4	88.5 ± 72.80	4.4–297.8
Ulnar Nerve	139	>5.0 mV	4.7 ± 2.94	0.2–11.3	93.8 ± 58.79	4.0–226.0
Tibial Nerve	140	>2.5 mV	4.9 ± 3.21	0.5–15.8	195.3 ± 128.49	20.0–632.0
Fibular Nerve	131	>2.5 mV	3.0 ± 2.33	0.2–12.6	121.2 ± 93.26	8.0–504.0

CMAP, compound muscle action potential.
* F-wave latency depends on subject's height.
Each of the four waveform parameters (distal latency, conduction velocity, F-wave latency and CMAP amplitude) are converted to percentages of normal values as per the AAN criteria.

Table 4
Conduct slowing of nerves in ALS. patients.

	Number of Nerves Studied	CV slowing in demyelinating range		*P*-value
		AAN	Equations	
Median Nerve	131	3.8%	3.8%	1.0000
Ulnar Nerve	135	0.7%	14.8%	<0.0001
Tibial Nerve	109	0.0%	10.1%	<0.0001
Fibular Nerve	124	0.8%	8.9%	0.0031
Total	**499**	**1.4%**	**9.4%**	**< 0.0001**
	Number of Nerves Studied	**Prolonged DL in demyelinating range**		***P*-value**
		AAN	**Equations**	
Median Nerve	133	3.8%	12.0%	0.0124
Ulnar Nerve	139	4.3%	12.2%	0.0168
Tibial Nerve	141	4.3%	14.9%	0.0024
Fibular Nerve	132	0.8%	7.6%	0.0056
Total	**545**	**3.3%**	**11.7%**	**< 0.0001**
	Number of Nerves Studied	**Prolonged F in demyelinating range**		***P*-value**
		AAN	**Equation**	
Median Nerve	87	23.0%	49.4%	0.0005
Ulnar Nerve	94	16.0%	28.7%	0.0533
Tibial Nerve	99	7.1%	18.2%	0.0308
Fibular Nerve	87	18.4%	31.0%	0.0781
Total	**367**	**15.8%**	**31.3%**	**< 0.0001**

AAN, American Academy of Neurology; CV, conduction velocity; DL, distal latency; F, F-wave latency; CMAP, compound muscle action potential.

number of abnormal F responses (41.2%) with normal corresponding DML and CV responses was significantly higher than the number of prolonged DML (11.2%) with normal corresponding CV and F, and the number of reduced CV (8.6.%) with normal corresponding DML and F ($p < 0.0001$).

In addition, there was no significant difference between the number of prolonged DML with normal corresponding CV and F response and the number of reduced CV with normal DML and F response.

The number of ALS patients with DML, CV, and F response slowing by the equations' ranges criteria alone, and by the equations' ranges criteria or AAN criteria combined is summarized in Table 5. No ALS patients had more than two motor nerves with conduction velocity slowing in the AAN or regression equation ranges. In ALS patients with two motor nerves or less in the demyelinating range, none of them has more than 4 DML or F responses in the demyelinating range either by regression equations or AAN criteria.

Linear regression analysis was performed to evaluate the association of CMAP amplitude as an independent variable and changes of distal latency, CV, or F responses as independent variables in the cohort of ALS patients. The results, as shown in Table 6, demonstrated

Table 5
The profile of conduction slowing in ALS patients.

CV/DL	DL0	DL1	DL2	DL3	F
CV0	31.6% (70.5%)	6.3% (11.6%)	2.1% (2.1%)	2.1% (2.1%)	**F0**
CV1	16.8% (18.9%)	5.3% (5.3%)	1.1% (2.1%)	3.2% (3.2%)	**F0**
CV2	1.1% (1.1%)	1.1% (1.1%)	1.1% (1.1%)	0% (0%)	**F0**
CV3	0% (0%)	0% (0%)	0% (0%)	0% (0%)	**F0**
CV0	6.3% (14.7%)	2.1% (3.2%)	0% (1.1%)	0% (0%)	**F1**
CV1	0% (0%)	3.2% (3.2%)	0% (0%)	1.1% (1.1%)	**F1**
CV2	0% (0%)	0% (0%)	0% (0%)	1.1% (1.1%)	**F1**
CV3	0% (0%)	0% (0%)	0% (0%)	0% (0%)	**F1**
CV0	0% (7.4%)	0% (0%)	1.1% (2.1%)	1.1% (1.1%)	**F2**
CV1	2.1% (3.2%)	2.1% (2.1%)	1.1% (1.1%)	0% (0%)	**F2**
CV2	0% (0%)	0% (0%)	0% (0%)	0% (0%)	**F2**
CV3	0% (0%)	0% (0%)	0% (0%)	0% (0%)	**F2**
CV0	0% (2.1%)	0% (0%)	2.1% (2.1%)	1.1% (1.1%)	**F3**
CV1	2.1% (2.1%)	0% (1.1%)	0% (0%)	0% (0%)	**F3**
CV2	0% (0%)	0% (0%)	0% (0%)	0% (0%)	**F3**
CV3	0% (0%)	0% (0%)	0% (0%)	0% (0%)	**F3**

CV, conduction velocity; DL, distal latency.
CV0, CV1, CV2 and CV3 correspond to patients with 0, at least 1, 2 and 3 motor nerves with CV in the equations' demyelinating range respectively.
DL0, DL1, DL2 and DL3 correspond to patients with 0, at least 1, 2 and 3 motor nerves with DL in the equations' demyelinating range respectively.
F0, F1, F2 and F3 correspond to patients with 0, at least 1, 2 and 3 motor nerves with F in the equations' demyelinating range respectively.
NOTE: The values in parentheses represent percentage of patients in demyelination range by either AAN or regression equations' criteria.

Table 6
Regression analysis of amplitude-dependent changes in distal latency, conduction velocity. and F response for ALS.

	Change in DL	Change in CV	Change in F
Median nerve (n)	122	121	62
Slope r	−0.133	0.141	−0.008
r[a]	−0.601	0.494	−0.357
P-value	<0.0001	<0.0001	0.0044
Ulnar nerve (n)	133	128	74
Slope	−0.368	1.018	−0.528
r[a]	−0.711	0.549	−0.286
P-value	<0.0001	<0.0001	0.0136
Tibial nerve (n)	135	104	88
Slope	−0.071	0.767	−0.004
r[a]	−0.352	0.369	−0.362
P-value	<0.0001	0.0001	0.0005
Fibular nerve (n)	119	112	59
Slope	−0.196	0.071	−0.040
r[a]	−0.398	0.272	−0.223
P-value	<0.0001	0.0018	0.0902

CV, conduction velocity; DL, distal latency; F, F-wave latency.
[a] Pearson correlation coefficient.

that there was significant CMAP-dependent CV slowing, and DML and F prolongation of all studied nerves except for F fibular and ulnar CV nerves.

4. Discussion

Although the diagnosis of ALS remains fundamentally clinical, electrodiagnostic testing has been unrivalled to date in providing evidence of clinical and subclinical lower motor neuron involvement and excluding other treatable neuromuscular conditions [18]. According to Gold Coast criteria, the presence of lower motor neurons dysfunction with evidence of ongoing active and chronic denervation in at least two body regions is supportive for the diagnosis of ALS when there is a progressive motor impairment, preceded by normal motor function and after the exclusion of other diseases [19].

Nerve conduction studies allow the exclusion of treatable neuropathies, such as multifocal motor neuropathy, motor CIDP or superimposed other neuropathies [20]. Our study demonstrated that no patients in the ALS group had more than two nerves with CV slowing in the demyelinating confidence interval defined by the regression equations validated by CIDP patients. When the AAN criteria for CIDP diagnosis were used in combination with these regression equations' criteria (patients with CV slowing in the demyelinating range by AAN criteria or in the demyelinating confidence interval defined by the regression equations) similar results were obtained. No patient in the ALS group had more than 2 nerves in the demyelination range. These findings suggest that an alternative diagnosis, or a superimposed demyelinating polyneuropathy, should be considered for patients suspected of having ALS

when such slowing is observed.

Although CV slowing in the AAN demyelination range was higher in the median nerve compared to the ulnar nerve, the overall incidence of CV slowing was higher in the ulnar nerve (combined AAN and regression analysis CV slowing, Table 3). This may suggest the presence of carpal tunnel syndrome (CTS) or a coexisting CTS with median to ulnar communication (MUC). Recently, the neurophysiological profile of MUC in CTS was investigated. The authors demonstrated a positive correlation between the severity of CTS and the presence of positive onset, faster CV, or a double component of the CMAP of the median nerve [21]. However, none of the above findings were observed in our study. Furthermore, the incidence of prolonged DML was not significantly higher in the median nerve compared to the ulnar nerve in our study.

Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv) can mimic ALS, particularly in the predominantly or purely motor neuropathy as well as in the case of thenar muscles weakness and hypotrophy related to CTS which is frequently observed in early stage ATTRv [14,22,23]. A recent study investigated motor conduction studies and handgrip in 20 patients with ATTRv. It demonstrated a significant prolongation of DML, reduction of MCV and handgrip strength in the ATTRv group compared to the control group [23]. In our study, although conduction slowing occurred in our ALS patients, it was associated with clinical and neurophysiological findings fulfilling the Escorial revised criteria of the World Federation of Neurology for ALS and making a misdiagnosed ATTRv very unlikely.

Because the regression equations were designed to achieve the best linear relationship between the CMAP amplitude of the corresponding CV, the resulting confidence interval may not include some severe conduction slowing. However, all CV slowing outside the equations' confidence intervals were in the AAN demyelinating range. Therefore, our regression equations' demyelinating confidence intervals may not be a substitute to the AAN criteria, but a complement to capture the electrodiagnostic data from patients with primary demyelination not severe enough to fulfill the AAN demyelination criteria [15].

In 1957, Lambert and Mulder used raw electrodiagnostic data to demonstrate a reduction of CV and mild prolongation of distal latency when the CMAP amplitude was severely reduced in ALS patients [24]. They also showed a parabolic relationship between raw CMAP amplitude data plotted against the corresponding CV from ALS patients [24]. Later, Cornblath et al. used square root transformation (SQRT) of raw data for a group of 61 ALS patients to achieve a better linear relationship between CMAP amplitude and corresponding DML, CV, and F latencies [6]. They were able to validate 8 of the 9 calculated regression equations and confidence intervals defining the range of slowing expected from a primary motor axonal loss [6]. A similar strategy was used by Feinberg et al. to demonstrate that the loss of large fast conducting fibers is the major mechanism of conduction slowing in ALS [7]. In the present study, we used SQRT initially. However, we found that the combination of SQRT, fourth root transformation, and Log_{10} transformation combination of the normalized data achieved the best linear relationship between CMAP amplitude and CV, DML, and F parameters in CIDP patients. This is most likely due to the broader range of variation of electrodiagnostic parameters in CIDP compared to ALS patients.

Several mechanisms have been proposed to explain conduction slowing in axonal neuropathy. Loss of large, myelinated fiber is the favored mechanism when conduction slowing is observed in the distal, intermediate, and proximal segments of the nerve. Segmental demyelination secondary to dying back of the most distal part of the nerve with slower conduction in the distal regenerating fibers is the mechanism when prolonged DML is observed with preservation of CV and F-wave latency. Motor root dysfunction is the major mechanism of conduction slowing when there is a preferential prolongation of the conduction time of the proximal segment of the motor nerve [3,7,25].

The current study demonstrates a CMAP amplitude dependent conduction slowing in ALS patients: there is a correlation between CMAP amplitude and CV, DML, and F latencies in the studied motor nerves (except fibular motor F and ulnar nerve conduction velocity). Moreover, reduced CV was associated with abnormal F and/or DML responses in most studied nerves and there is no preferential conduction slowing in the distal, intermediate, or proximal parts of the motor nerve. In addition, conduction slowing in the AAN range was observed in respectively 1.4% and 3.3% of studied motor nerves CV and DML and no patient fulfilled the AAN or EFNS/PNS criteria for the diagnosis of CIDP [15,26]. These findings suggest that loss of large axons is the main mechanism of conduction slowing in ALS patients when Escorial diagnosis criteria are fulfilled, although a secondary demyelination from a primary axonal loss cannot be excluded. Conduction slowing from loss of large, myelinated fibers in ALS patients was also reported by Herrmann et al. as well as Feinberg et al. when they used SQRT to study the relationship between CMAP amplitude and velocity parameters [7,27] However, a selective vulnerability of large, myelinated fibers in ALS is controversial [28–30].

We found in the current study that only 11.2% of motor nerves with prolonged DML had preserved corresponding CV and F responses, suggesting that distal axonopathy is less likely the predominant mechanism of conduction slowing in ALS. Several studies have reported CV slowing in the distal part of the motor neuron, even in mildly affected nerves. This was attributed to conduction slowing in thin distal regenerated motor axons as well as to a defect in neuromuscular transmission [3,25,31].

An abnormal F response with a normal corresponding DML and CV was observed in 41.2% of F latencies in this study, suggesting proximal segment slowing as the most likely mechanism of conduction slowing in these nerves. Several studies reported similar findings. Ertas et al. evaluated the H and F responses in 11 ALS patients. They reported a delay in the dorsal-to-ventral root potential interval in ALS patients compared with normal controls and poliomyelitis patients [32]. Increased proximal motor nerve conduction time, including increased F wave dispersion and latencies has been reported in ALS patients by de Carvalho et al. as well as by other authors [3,33–36]. Impaired motor neuron axoplasmic transport with neurofilament accumulation in the proximal segments has also been advanced to explain the selective conduction slowing in the proximal motor nerves in ALS [32].

This study suggests that loss of large, myelinated motor fibers is likely the predominant mechanism of conduction slowing in ALS, although selective distal axonopathy and proximal motor nerve dysfunction have been observed in a few motor nerves. The mechanism of conduction slowing in ALS may depend on the stage of the disease and the molecular mechanism underlying the motor nerve injury.

All patients included in this study fulfilled the Escorial criteria for ALS and were not in the early stage of the disease. Loss of large fibers and distal axonopathy with sprouting of distal terminals may occur at an advanced stage of the disease, whereas proximal conduction dysfunction may occur at an earlier stage. This is supported by the work of de Carvalho et al. who reported anterior horn cell membrane instability in the early stage of ALS, and by the work of Ertas et al. who demonstrated proximal conduction slowing in patients in the early stages of illness [32,37].

Our study was limited to ALS patients that fulfilled Escorial revised criteria of the World Federation of Neurology [16] where widespread lower motor neuron degeneration is observed and acquired secondary demyelination from a primary axonal loss may occur. Electrodiagnostic testing of ALS and its variants at different stages of the disease combined with the use of our novel regression analysis may better characterize conduction slowing in ALS and identify a primary demyelination.

5. Conclusion

Mild-to-moderate conduction slowing in ALS patients, not fulfilling the AAN research criteria for CIDP diagnosis, may be predominantly related to loss of large, myelinated fibers.

The current study demonstrated that regression analysis equations, derived from a well-defined group of CIDP patients, when applied to a group of well characterized ALS patients, results in regressions that can provide electrodiagnostic insights beyond those inferred by examining conventional electrodiagnostic parameters. For a given CMAP, the regression equations identified demyelinating range conduction slowing confidence interval expected from a primary acquired demyelination. The presence of more than two motor nerves with conduction velocity slowing in the demyelinating range, either by the AAN criteria or by the regression criteria suggests an alternative diagnosis or superimposed demyelination. Combined with the AAN criteria, this new criteria for acquired demyelination can be useful to differentiate the classic form of ALS from inflammatory neuropathies. Furthermore, these new criteria in combination with clinical examination could be used to differentiate axonal neuropathy from a mild or atypical CIDP.

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Author contribution statement

Nizar Souayah: Conceived and designed the experiments: Wrote the paper.
Ankit Pahwa, Tejas Patel and Bu Nasr: Analyzed and interpreted the data.
Mustafa Jaffry and Hoard Dander: Performed the experiments.
Zhao Zhong Chong: Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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References

[1] E.L. Feldman, S.A. Goutman, S. Petri, L. Mazzini, M.G. Savelieff, P.J. Shaw, G. Sobue, Amyotrophic lateral sclerosis, Lancet 400 (10360) (2022) 1363–1380.
[2] R.P.A. van Eijk, A.R. Jones, W. Sproviero, A. Shatunov, P.J. Shaw, P.N. Leigh, C.A. Young, C.E. Shaw, G. Mora, J. Mandrioli, et al., Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis clinical trials, Neurology 89 (18) (2017) 1915–1922.
[3] M. de Carvalho, M. Swash, Nerve conduction studies in amyotrophic lateral sclerosis, Muscle Nerve 23 (3) (2000) 344–352.
[4] D.J. Lange, W. Trojaborg, N. Latov, A.P. Hays, D.S. Younger, A. Uncini, D.M. Blake, M. Hirano, S.M. Burns, R.E. Lovelace, et al., Multifocal motor neuropathy with conduction block: is it a distinct clinical entity? Neurology 42 (3 Pt 1) (1992) 497–505.
[5] D.J. Lange, W. Trojaborg, T.D. McDonald, D.M. Blake, Persistent and transient "conduction block" in motor neuron diseases, Muscle Nerve 16 (9) (1993) 896–903.
[6] D.R. Cornblath, R.W. Kuncl, E.D. Mellits, S.A. Quaskey, L. Clawson, A. Pestronk, D.B. Drachman, Nerve conduction studies in amyotrophic lateral sclerosis, Muscle Nerve 15 (10) (1992) 1111–1115.
[7] D.M. Feinberg, D.C. Preston, J.M. Shefner, E.L. Logigian, Amplitude-dependent slowing of conduction in amyotrophic lateral sclerosis and polyneuropathy, Muscle Nerve 22 (7) (1999) 937–940.
[8] C.P. Douglass, R.H. Kandler, P.J. Shaw, C.J. McDermott, An evaluation of neurophysiological criteria used in the diagnosis of motor neuron disease, J. Neurol. Neurosurg. Psychiatr. 81 (6) (2010) 646–649.

[9] M. Higashihara, M. Sonoo, [Electrodiagnosis of ALS], Brain and nerve = Shinkei kenkyu no shinpo 59 (10) (2007) 1031–1041.
[10] D.A. Chad, Electrodiagnostic approach to the patient with suspected motor neuron disease, Neurol. Clin. 20 (2) (2002) 527–555 (viii).
[11] J.M. Belsh, Diagnostic challenges in ALS, Neurology 53 (8 Suppl 5) (1999) S26–S30, discussion S35-26.
[12] T. Evangelista, M. Carvalho, I. Conceicao, A. Pinto, M. de Lurdes, M.L. Luis, Motor neuropathies mimicking amyotrophic lateral sclerosis/motor neuron disease, J. Neurol. Sci. 139 (Suppl) (1996) 95–98.
[13] N. Singh, S. Ray, A. Srivastava, Clinical mimickers of amyotrophic lateral sclerosis-conditions we cannot afford to miss, Ann. Indian Acad. Neurol. 21 (3) (2018) 173–178.
[14] P. Lozeron, C. Lacroix, M. Theaudin, A. Richer, M. Gugenheim, D. Adams, M. Misrahi, An amyotrophic lateral sclerosis-like syndrome revealing an amyloid polyneuropathy associated with a novel transthyretin mutation, Amyloid 20 (3) (2013) 188–192.
[15] Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from an ad Hoc subcommittee of the American Academy of Neurology AIDS task force, Neurology 41 (5) (1991) 617–618.
[16] B.R. Brooks, R.G. Miller, M. Swash, T.L. Munsat, D. World Federation of Neurology Research, Group on Motor Neuron. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis, Amyotroph Lateral Scler. 1 (5) (2000) 293–299.
[17] J. Kimura, Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice, FA Davis, 1989.
[18] M.R. Turner, U.M.C.S. Group, Diagnosing ALS: the Gold Coast criteria and the role of EMG, Practical Neurol. 22 (3) (2022) 176–178.
[19] S. Vucic, T.A. Ferguson, C. Cummings, M.T. Hotchkin, A. Genge, R. Glanzman, K.C.D. Roet, M. Cudkowicz, M.C. Kiernan, Gold Coast diagnostic criteria: implications for ALS diagnosis and clinical trial enrollment, Muscle Nerve 64 (5) (2021) 532–537.
[20] N.C. Joyce, G.T. Carter, Electrodiagnosis in persons with amyotrophic lateral sclerosis, Pharm. Manag. PM R 5 (5 Suppl) (2013) S89–S95.
[21] V. Di Stefano, A. Gagliardo, F. Barbone, M. Vitale, L. Ferri, A. Lupica, S. Iacono, A. Di Muzio, F. Brighina, Median-to-Ulnar nerve communication in carpal tunnel syndrome: an electrophysiological study, Neurol. Int. 13 (3) (2021) 304–314.
[22] J.P. Donnelly, M. Hanna, B.W. Sperry, W.H. Seitz Jr., Carpal tunnel syndrome: a potential early, Red-Flag sign of amyloidosis, J. Hand. Surg. Am. 44 (10) (2019) 868–876.
[23] V. Di Stefano, E. Thomas, V. Giustino, S. Iacono, A. Torrente, G. Pillitteri, A. Gagliardo, A. Lupica, A. Palma, G. Battaglia, F. Brighina, Motor conduction studies and handgrip in hereditary TTR amyloidosis: simple tools to evaluate the upper limbs, Front. Neurol. 13 (2022), 835812.
[24] E.H. Lambert, D.W. Mulder, Electromyographic studies in amyotrophic lateral sclerosis, Proc. Staff Meet. Mayo Clin. 32 (17) (1957) 441–446.
[25] B. Mohammadi, K. Krampfl, K. Kollewe, A. Seyfadini, J. Bufler, R. Dengler, Correlation between distal motor latency and compound muscle action potential in amyotrophic lateral sclerosis, Neurol. Res. 29 (5) (2007) 425–428.
[26] P.Y. Van den Bergh, R.D. Hadden, P. Bouche, D.R. Cornblath, A. Hahn, I. Illa, C.L. Koski, J.M. Leger, E. Nobile-Orazio, J. Pollard, et al., European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision, Eur. J. Neurol. 17 (3) (2010) 356–363.
[27] D.N. Herrmann, M.L. Ferguson, E.L. Logigian, Conduction slowing in diabetic distal polyneuropathy, Muscle Nerve 26 (2) (2002) 232–237.
[28] W.G. Bradley, P. Good, C.G. Rasool, L.S. Adelman, Morphometric and biochemical studies of peripheral nerves in amyotrophic lateral sclerosis, Ann. Neurol. 14 (3) (1983) 267–277.
[29] T. Nakanishi, M. Tamaki, K. Arasaki, Maximal and minimal motor nerve conduction velocities in amyotrophic lateral sclerosis, Neurology 39 (4) (1989) 580–583.
[30] M. Iijima, K. Arasaki, H. Iwamoto, T. Nakanishi, Maximal and minimal motor nerve conduction velocities in patients with motor neuron diseases: correlation with age of onset and duration of illness, Muscle Nerve 14 (11) (1991) 1110–1115.
[31] Y. Noto, K. Kanai, S. Misawa, K. Shibuya, S. Isose, S. Nasu, Y. Sekiguchi, Y. Fujimaki, M. Nakagawa, S. Kuwabara, Distal motor axonal dysfunction in amyotrophic lateral sclerosis, J. Neurol. Sci. 302 (1–2) (2011) 58–62.
[32] M. Ertas, B. Uludag, C. Ertekin, Slow motor conduction mainly limited to motor root in amyotrophic lateral sclerosis, Muscle Nerve 19 (8) (1996) 1003–1008.
[33] C.J. Argyropoulos, C.P. Panayiotopoulos, S. Scarpalezos, F- and M-wave conduction velocity in amyotrophic lateral sclerosis, Muscle Nerve 1 (6) (1978) 479–485.
[34] J.H. Petajan, F-waves in neurogenic atrophy, Muscle Nerve 8 (8) (1985) 690–696.
[35] K.J. Felice, Nerve conduction velocities of single thenar motor axons based on the automated analysis of F waves in amyotrophic lateral sclerosis, Muscle Nerve 21 (6) (1998) 756–761.
[36] R.M. Koutlidis, J. de Recondo, N. Bathien, Conduction of the sciatic nerve in its proximal and distal segment in patients with ALS (amyotrophic lateral sclerosis), J. Neurol. Sci. 64 (2) (1984) 183–191.
[37] M. de Carvalho, M. Swash, Fasciculation potentials: a study of amyotrophic lateral sclerosis and other neurogenic disorders, Muscle Nerve 21 (3) (1998) 336–344.