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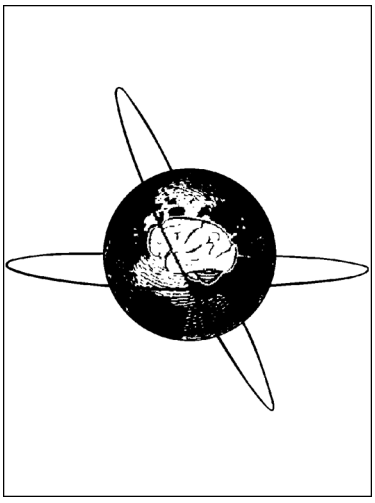

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Peripheral nerve electrophysiology studies in relation to fatigue in patients with chronic inflammatory demyelinating polyneuropathy

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Abstract

Objective: To explore the relationship between fatigue, standard electrophysiological parameters and number and size of functioning motor units in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: Experienced fatigue was assessed using the linearly-weighted, modified Rasch-built fatigue severity scale (R-FSS) and the multidimensional Checklist of Individual Strength (CIS). Averaged electrophysiology values were calculated from multiple nerves. Motor Unit Number Index (MUNIX) technique was utilised to assess motor unit function. Assessments were repeated in 15 patients receiving regular intravenous immunoglobulin therapy, with changes in parameters calculated.

Results: R-FSS and CIS scores did not correlate MUNIX or MUSIX sum scores from 3 different muscles. Inverse correlation was observed only between distal CMAP area and R-FSS but not CIS scores. However, changes in distal CMAP area and R-FSS scores on repeat assessment were not correlated.

Conclusions: Experienced fatigue does not appear to correlate with loss of functioning motor units in patients with CIDP. Changes in experienced fatigue on repeat assessment did not correlate with changes in any of the electrophysiological parameters, suggesting fatigue experienced in CIDP is not strongly correlated with peripheral nerve dysfunction.

Significance: Nerve conduction studies and MUNIX values do not appear to be useful surrogate markers for fatigue in CIDP

Highlights

- Experienced fatigue does not correlate with MUNIX or MUSIX sum scores in CIDP
- Only CMAP area significantly correlated with experienced fatigue level on initial assessment
- Change in fatigue level on repeat assessment did not correlate with changes in commonly used electrophysiology parameters

Keywords

Fatigue
CIDP
MUNIX
Nerve conduction studies

1. Introduction

Fatigue is a recognised feature of a wide-range of neurological disorders (Chaudhuri and Behan 2004). The term fatigue usually refers to the physical or mental experience of a lack of energy or motivation, although perhaps unsurprisingly given its inherently subjective nature, no universally agreed definition of fatigue exists in the scientific literature (Gandevia 2001; Zwarts et al. 2008). Assessment of the individual experience of fatigue, referred to as experienced fatigue, utilises self-report psychometric scales to assess either fatigue levels or the impact of fatigue on daily functioning (Dittner et al. 2004).

Experienced fatigue may occur as a residual symptom even after otherwise good clinical recovery from Guillain-Barré Syndrome (GBS) or as part of chronic immune-mediated neuropathies (Merkies et al. 1999; Garssen et al. 2006c; Kuitwaard et al. 2009). Severe experienced fatigue is reported to occur more frequently and inversely correlate with quality of life scores in both acute and chronic immune-mediated neuropathies (Merkies et al. 1999; Bussmann et al. 2007; Kuitwaard et al. 2009; Rekand et al. 2009; Westblad et al. 2009). As a result, some authors have called for greater recognition of fatigue and further study to determine effective treatment strategies (Merkies and Kieseier 2016).

A major limitation is that pathophysiology of fatigue in peripheral nerve disorders is poorly understood. Fatigue can occur independently of other markers of disease severity and does not appear to correlate with clinical assessments of sensory or motor function (Merkies et al. 1999; Garssen et al. 2006c; Drenthen et al. 2013). Several studies have also demonstrated that residual fatigue following GBS does not correlate with standard electrophysiological measures of peripheral nerve function (Garssen et al. 2006b, 2006a). A single study utilising motor unit number estimation (MUNE) has suggested that patients with severe residual fatigue following GBS have more pronounced axonal loss and larger size of surviving motor units compared to non-fatigued patients (Drenthen et al. 2013). It is hypothesised that greater loss and subsequent re-innervation affects orderly recruitment of motor units (Henneman et al. 1965), possibly leading to fatigue (Drenthen et al. 2013). However, to our knowledge no similar explorations have been made in patients with chronic immune-mediated neuropathies.

This study involves a cohort of patients described previously (Lawley et al. 2019). The aim of this component of the study was to explore the relationship between experienced fatigue, standard electrophysiological parameters and number and size of functioning motor units in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

2. Methodology

2.1. Subjects

Patients attending a specialist Inflammatory Neuropathy Clinic at the Queen Elizabeth Hospital, Birmingham, were invited to participate, irrespective of treatment status. Inclusion criteria were diagnosis of "definite" or "probable" CIDP as per European Federation of Neurological Societies/Peripheral Nerve Society Guidelines (van den Bergh et al., 2010) and age 18-85 years. Exclusion criteria included co-morbid conditions which could contribute to fatigue; known malignancy, psychiatric diagnosis preceding onset of the neuropathy, anaemia, hypothyroidism, obstructive sleep apnoea, cardiac or pulmonary disorders. All thirty-four patients meeting inclusion criteria were invited with 8 declining.

Written consent was provided by all patients and this study has ethical approval from the NHS Health Research Authority (IRAS no. 206150).

2.2. Fatigue assessments

Experienced fatigue was assessed using the linearly-weighted, modified Rasch-built fatigue severity scale (R-FSS) (van Nes et al. 2009). This scale was developed from the Fatigue Severity Scale (Krupp et al. 1989) for use in patients with immune-mediated neuropathy. R-FSS scores range from 0-21. In addition, the checklist of individual strength (CIS) was used to provide a multidimensional assessment of patients' experience of fatigue (Vercoulen et al. 1994; Beurskens et al. 2000; Kalkman et al. 2005). Overall CIS scores range from 0-140. In both R-FSS and CIS, higher scores relate to higher fatigue levels.

2.3. Nerve conduction studies

Nerve conduction studies (NCS) were performed by the same author (AL), with skin surface temperature raised to above 32°C in the hands and 30°C in the feet if required. Studies were performed unilaterally using disposable surface electrodes. Measurements of sensory nerve action potential (SNAP) amplitude and sensory nerve conduction velocity were performed from sural and superficial radial nerves (antidromic studies) and median and ulnar nerves (orthodromic studies). Motor NCS measured distal motor latency (DML), onset-to-peak amplitude, negative peak area, negative peak duration, conduction velocities, minimum F-wave latency and F-wave persistence for each nerve tested. Recording and stimulation sites were as follows; median nerve recording from abductor pollicis brevis (APB) and stimulating at the wrist, elbow and axilla, ulnar nerve recording from abductor digiti minimi (ADM) and stimulating at the wrist, below the elbow, above the elbow and axilla, tibial nerve recording from abductor hallucis (AH) and stimulating posterior to the medial malleolus and popliteal fossa, and peroneal nerve recording from extensor digitorum brevis (EDB) and stimulating at the ankle, below and above the fibular head.

Average values for each parameter in individual patients were calculated by summation then division by the number of nerves from which values could be recorded. For example, if DML could be recorded from peroneal, tibial, median and ulnar nerves, the DML for each nerve was summated then divided by 4. If CMAPs could only be recorded from 3 nerves, the three responses were summated and divided by 3. Conduction velocities were calculated from distal nerve segments. Proximal-evoked potential refers to the most proximal CMAP that could be elicited.

2.4. MUNIX

MUNIX studies were carried out in accordance with protocols described by Neuwirth and colleagues (Neuwirth et al. 2010) using a Dantec™ Keypoint® Focus machine. Motor unit size index (MUSIX) was calculated by dividing CMAP amplitude by MUNIX. MUNIX and MUSIX sum scores were calculated unilaterally from APB, ADM and tibialis anterior (TA) muscles. Electrode placement is described previously (Lawley et al. 2019). Sum scores were calculated as these have been shown to have better correlation with clinical data (Neuwirth et al. 2010; Delmont et al. 2016; Grimaldi et al. 2017).

2.5. Statistical analysis

To our knowledge, no previous studies have assessed correlation between fatigue scales and electrophysiology studies in this patient population. Previous work found correlation coefficients of between 0.61 and 0.71 when exploring the relationship between MUNIX sum scores, clinical assessments and disability scores. Assuming similar coefficients, a sample size of 26 patients would be required using α of 0.004 and β of 90% (Bland 2000).

Fatigue scores demonstrated nonparametric distribution. Data are presented as median values (interquartile range), with the exception of MUNIX and MUSIX values presented as mean (standard deviation). Correlation analysis was performed using Spearman's Rank correlation. After Bonferroni correction for multiple comparisons an alpha value of ≤ 0.004 was considered significant. All statistical analysis was performed using IBM SPSS statistical software (version 25).

3. Results

3.1. Demographics

Twenty-six patients were included (5 female; age range 49–79y; mean age 62.5y). There was an average of 61 months between diagnosis of CIDP and enrolment. Patients were stable on current treatment; 15 undergoing regular intravenous immunoglobulin (IVIg) therapy alone at 3 to 6 weekly intervals; 1 receiving subcutaneous immunoglobulins alone and 10 receiving physiotherapy input only. No changes were made to treatment as part of this study. All 15 patients receiving IVIg therapy had an initial assessment 2 to 3 days prior to IVIg therapy and between 11 and 21 days (average 15±4 days)

after the infusion. The rationale for this interval was to time repeat assessments to coincide with "peak effect" following IVIg therapy (Pollard and Armati 2011), with patients with a shorter interval between IVIg infusions seen earlier for repeat assessment. Further clinical details of this patient cohort are described previously (Lawley et al. 2020).

3.2. Experienced fatigue

Median R-FSS score in CIDP patients was 17 out of 21 (13.5-19) and median overall CIS score was 77.5 out of 140 (61-98.8). Median scores in CIS subdomains were; subjective feeling of fatigue 40 (33-47.3), concentration 12.5 (7.5-18), motivation 13.5 (9.5-16.8) and physical activity 12 (7.3-17). R-FSS and CIS scores were also repeated in 15 patients receiving IVIg therapy (see table 1).

3.3. Nerve conduction studies and MUNIX

Nerve conduction studies were performed once in all patients and repeated in 14 of the 15 patients receiving regular IVIg therapy. One patient consented to repeat MUNIX assessment but declined repeat nerve conduction studies. Data for all patients and repeat assessments are provided in table 2.

MUNIX and MUSIX values have been reported previously in this cohort (Lawley et al. 2019). Average MUNIX sum score in the whole patient cohort was 214.0 (124.4) and average MUSIX sum score was 251.2 (96.2). In 15 patients receiving regular IVIg therapy average MUNIX sum score was 188.3 (110.5) before IVIg and 266.4 (132.0) on repeat assessment after IVIg. Average MUSIX sum score was 266.5 (84.7) before IVIg and 253.5 (99.9) on repeat assessment after IVIg.

3.4. Correlation analysis

Neither R-FSS or overall CIS scores showed significant correlation with MUNIX or MUSIX sum scores. Spearman's Rank correlation coefficient for R-FSS and MUNIX was -0.330 (*p=0.100*), R-FSS and MUSIX 0.073 (*p=0.721*), CIS and MUNIX -0.319 (*p=0.113*) and CIS and MUSIX 0.004 (*p=0.984*).

A statistically significant correlation was observed between R-FSS score and area of the distal CMAP (r=-0.552, *p=0.003*). Similar correlation coefficients were observed between R-FSS scores and amplitude of the distal CMAP (r=-0.516, *p=0.007*), amplitude of the proximal CMAP (r=-0.482, *p=0.013*) and area of the proximal CMAP (r=-0.523, *p=0.006*), although these did not meet pre-defined statistical significance (see figure 1). No significant correlation was observed between overall CIS scores and any of the electrophysiological parameters. Full details of correlation analysis are provided in table 3.

Given the associations seen at first assessment, changes in R-FSS scores on repeat assessment were correlated with changes in amplitude and area of the distal CMAP and amplitude and area of the proximal CMAP in 14 of the patients receiving regular IVIg therapy. Spearman's Rank correlation coefficient for ΔR-FSS and Δdistal CMAP area was -0.117 (*p=0.690*). In addition, no statistically significant correlations were observed between ΔR-FSS and the other parameters.

4. Discussion

Distally-evoked CMAP area showed modest inverse correlation with one of the scales used to assess experienced fatigue. Similar correlations were seen with distal CMAP amplitude and proximal CMAP amplitude and area, albeit not reaching statistical significance. No significant correlation was observed with parameters primarily reflecting nerve demyelination, including DML, conduction velocities or F-wave latency. These observations may suggest more pronounced axonal loss in CIDP is associated with more severe fatigue. However, similar correlations were not seen between these parameters and a second fatigue scale and changes in CMAP area did not correlate with changes in fatigue scores on repeat assessments. In addition, this hypothesis would be inconsistent with lack of correlation with MUNIX or MUSIX sum scores.

This study utilised averaged electrophysiological parameters from several nerves, rather than values from individual nerves. Improvements in proximal CMAP amplitudes from individual nerves have been described in patients responding to IVIg (Ashworth et al. 2000). However, other studies report that summary parameters (either summated or averaged values) may be more sensitive than relying on values obtained from individual nerves alone (Dyck et al. 1994; Bril et al. 2009). This may be particularly relevant in CIDP where patchy and selective nerve involvement can be observed. Analysis based on the most severely affected nerve may overestimate severity of axonal loss and nerve demyelination, whereas analysis of nerves from which parameters can easily be recorded may result in an underestimate. Use of averaged electrophysiological parameters provides a more "global" measure of peripheral nerve dysfunction. Using this method, nerve conduction studies did not strongly correlate with experienced fatigue levels in CIDP. Similar findings are reported in patients with severe residual fatigue following GBS when analysing nerve conduction studies of individual nerves (Garssen et al. 2006b).

In a study utilising multi-point stimulation MUNE, residual fatigue following GBS was found to be more severe in patients with more pronounced axonal loss (Drenthen et al. 2013). We did not find a similar relationship in patients with CIDP using MUNIX. This may reflect the use of different assessment methods (Neuwirth et al. 2011). Some authors have suggested CMAP amplitude has a greater influence on MUNIX and MUSIX than number or size of functioning motor units (Jacobsen et al. 2018;

Bostock et al. 2019). However, other studies suggest MUNIX is strongly correlated and non-inferior to incremental stimulation and high-density MUNE techniques (Boekestein et al. 2012; Furtula et al. 2013). The reasons for the lack of correlations of R-FSS with both CMAP and MUNIX, remain hence ultimately, uncertain.

An alternative explanation for the different finding in CIDP patients may be different pathophysiology underlying fatigue in patients with acute and chronic neuropathies. Studies in patients with Charcot-Marie Tooth disease have demonstrated lower movement-related cortical potentials in the primary motor area and larger prefrontal activity during isometric knee extension exercises (Menotti et al. 2014). Greater central activation failure is reported in a small cohort of patients with recovered GBS compared to controls during sustained biceps brachii contraction (Garssen et al. 2007). Increased cognitive effort may be a compensatory mechanism to maintain muscle strength despite peripheral nerve dysfunction. Further study is required to determine whether fatigue may result from central maladaptation to peripheral deficits in patients with CIDP.

CIDP may affect nerves supplying proximal and distal muscles (Vallat et al. 2010). However, this study calculated MUNIX and MUSIX sum scores from distal muscles. MUNIX assessment of proximal muscles is more challenging. Techniques to study the musculocutaneous nerve recording from biceps brachii are reported although technical errors may occur due to nerve co-stimulation (Neuwirth et al. 2018). It is possible that study of an additional proximal muscle may have improved overall assessment for correlation with fatigue scores.

A further interesting observation is greater increase in MUNIX sum scores (41%) on repeat assessment following IVIg therapy compared to the other electrophysiological parameters, including distal CMAP amplitude (14%) and area (7%). MUNIX technique requires voluntary activation of muscles, requiring an intact motor pathway. Recording a distal CMAP requires only the distal part of the motor pathway to be intact. This observation may therefore reflect “unblocking” of proximal conduction block, which would affect MUNIX values but not the distal CMAP. Erb’s point stimulation was not performed in this study due to potential for submaximal stimulation, although interestingly an increase in average F-wave persistence from 45 to 70% was observed following IVIg. The clinical significance of increase in MUNIX sum scores and possible explanations for this have been discussed previously (Lawley et al. 2019).

One limitation of this study is the relatively small sample size, particularly for patients undergoing repeat assessments. A conservative alpha value of 0.004 was accepted for correlation analysis given that multiple comparisons were made. Previous studies have found correlation coefficients between 0.61 and 0.71 when exploring the relationship between MUNIX sum scores, clinical assessments such

as MRC muscle strength and disability scales such as Overall Neuropathy Limitations Scale (Delmont et al. 2016; Lawley et al. 2019). Sample size calculation suggests this study is sufficiently powered to detect similar correlations between the electrophysiology parameters and fatigue scales used in this study, but it is difficult to confidently exclude weaker correlations. A further potential limitation of this study is that MUNIX assessments suffer from "floor effect" when few motor units are supplying a muscle and patients are able to exert little force. This may impact ability to detect associations in patients with more severe disease. We invited all eligible participants to the study and as a result reduced potential selection bias. However, our patients all attended a tertiary inflammatory neuropathy service, as opposed to general neurology services. We otherwise did not use other electrophysiological methods such as repetitive nerve stimulation in this study, as we did not consider investigation of the neuromuscular junction of relevance in CIDP in relation to fatigue.

5. Conclusion

No significant relationship was found between fatigue levels and number or size of functioning motor units in patients with CIDP Distal CMAP area showed modest inverse correlation with one of the fatigue scales, although changes in this parameter did not relate to changes in fatigue scores on repeat assessments. As such, peripheral nerve dysfunction explored using electrophysiology studies does not appear to explain level of experienced fatigue in this study. These findings suggest nerve conduction studies and MUNIX technique are unlikely to be useful surrogate markers for fatigue in CIDP. Further studies are required to understand mechanisms of fatigue in CIDP, which remains a genuine and difficult problem for patients.

Conflict of interest

The authors have no conflict of interests to declare.

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Table 1

Rasch-built fatigue severity scale (R-FSS) and Checklist of Individual Strength (CIS) scores. Repeat assessments were performed in chronic inflammatory demyelinating polyneuropathy (CIDP) patients on regular intravenous immunoglobulin (IVIg) therapy. Data presented as median values (inter-quartile range).

Fatigue assessment scale	**CIDP whole cohort (*n=26*)**	**CIDP IVIg group (*n=15*)**	
		Pre-IVIg	Repeat
R-FSS	17 (13.5-19)	17 (14-19.5)	16 (11.5-17.5)
CIS overall	77.5 (61-98.8)	75 (66.5-104)	79 (63.5-94)
CIS subjective	*40 (33-47.3)*	*40 (33-45)*	*39 (35-49)*
CIS concentration	*12.5 (7.5-18)*	*14 (8-19.5)*	*14 (8-17.5)*
CIS motivation	*13.5 (9.5-16.8)*	*15 (11-16.5)*	*13 (8.5-15)*
CIS physical activity	*12 (7.3-17)*	*16 (8.5-19)*	*12 (9.5-16.5)*

Table 2

Averaged electrophysiology parameters. Repeat assessments were performed in chronic inflammatory demyelinating polyneuropathy (CIDP) patients on regular intravenous immunoglobulin (IVIg) therapy (one patient declined repeat nerve conduction studies). Data presented as median values (inter-quartile range). DML=distal motor latency, dCMAP=distal compound muscle action potential, EP=electrophysiology, NCV=nerve conduction velocity, pCMAP=proximal compound muscle action potential, SNAP=sensory nerve action potential.

Averaged EP parameters	**CIDP whole cohort *(n=26)***	**CIDP IVIg group (*n=14)***		
		pre-IVIg	Repeat	Δ
DML (ms)	5.7 *(4.7-6.8)*	6.4 *(5.2-6.9)*	6.1 *(4.9-7.2)*	-0.2 *(-0.3-0)*
dCMAP amplitude (mV)	5.4 *(2.7-5.9)*	*5.0 (3.1-5.6)*	5.7 *(3.7-6.2)*	0.3 *(0.1-0.6)*
dCMAP area (mV*ms)	14.9 *(8.6-17.7)*	*15.0 (11.2-17.5)*	16.7 *(10.7-17.0)*	1.0 *(-0.7-1.7)*
dCMAP duration (ms)	7.3 *(6.0-8.9)*	*7.5 (6.7-10.0)*	7.7 *(6.5-10.2)*	0.3 *(-0.6-0.8)*
pCMAP amplitude (mV)	3.4 *(1.6-4.7)*	*3.4 (0.8-4.2)*	3.5 *(0.9-4.1)*	0.1 *(-0.1-0.4)*
pCMAP area (mV*ms)	11.3 *(5.4-17.0)*	*10.3 (2.6-14.3)*	11.1 *(3.5-14.7)*	0.1 *(-1.7-1.2)*
pCMAP duration (ms)	7.7 *(6.8-10.2)*	*8.7 (7.2-9.3)*	7.5 *(6.5-8.9)*	-0.5 *(-1.0-0.1)*
Motor NCV (m/s)	38.9 *(33.0-43.1)*	*36.1 (25.5-41.6)*	37.8 *(27.3-40.2)*	1.1 *(-0.1-1.8)*
Min. F-wave latency (ms)	41.0 *(39.2-49.0)*	49.7 *(43.4-53.4)*	43.8 *(40.7-50.0)*	*-0.8 (-6.7-0.2)*
F-wave persistence (%)	56.7 *(38.3-74.2)*	45 *(35.8-60.0)*	70 *(55.0-81.5)*	15 *(7.5-28.3)*
SNAP amplitude (μV)	4.7 *(3.2-7.1)*	3.4 *(3.1-5.3)*	4.4 *(2.8-7.8)*	0.6 *(0.0-1.9)*
Sensory NCV (m/s)	42.5 *(37.9-45.9)*	32.1 *(28.2-38.9)*	36.4 *(26.9-42.3)*	0.8 *(-1.9-7.8)*

Table 3

Spearman Rank Correlation of experienced fatigue scales and electrophysiological parameters. Statistically significant correlations are highlighted in bold. CI=confidence interval, CIS=checklist of individual strength, DML=distal motor latency, dCMAP=distal compound muscle action potential, EP=electrophysiology, MUNIX=motor unit number index, MUSIX=motor unit size index, NCV=nerve conduction velocity, pCMAP=proximal compound muscle action potential, R-FSS=Rasch-built fatigue severity scale, SNAP=sensory nerve action potential.

	R-FSS			**Overall CIS score**		
	Correlation co-efficient	Significance (2-tailed)	95% CI	Correlation co-efficient	Significance (2-tailed)	95% CI
MUNIX	-0.330	*0.100*	*-0.66-0.14*	-0.319	*0.113*	*-0.64-0.11*
MUSIX	0.073	*0.721*	*-0.38-0.54*	0.004	*0.984*	*-0.40-0.47*
DML	0.165	*0.420*	-0.24-0.62	0.154	*0.451*	-0.27-0.52
dCMAP amplitude	-0.516	*0.007*	-0.79--0.09	-0.353	*0.077*	-0.65-0.04
dCMAP area	**-0.552**	***0.003***	**-0.80--0.12**	-0.346	*0.084*	-0.69-0.09
dCMAP duration	0.137	*0.503*	-0.29-0.50	0.035	*0.867*	-0.39-0.47
pCMAP amplitude	-0.482	*0.013*	-0.79--0.03	-0.245	*0.228*	-0.61-0.18
pCMAP area	-0.523	*0.006*	-0.80--0.13	-0.224	*0.272*	-0.62-0.20
pCMAP duration	0.007	*0.973*	-0.42-0.44	-0.077	*0.709*	-0.47-0.33
Motor NCV	-0.312	*0.120*	-0.67-0.11	-0.222	*0.275*	-0.57-0.16
Min F-wave latency	0.132	*0.560*	-0.12-0.21	-0.046	*0.840*	-0.45-0.38
F-wave persistence	-0.239	*0.285*	-0.62-0.18	-0.098	*0.663*	-0.48-0.30
SNAP amplitude	0.006	*0.978*	-0.46-0.43	-0.002	*0.992*	-0.44-0.43
Sensory NCV	0.217	*0.333*	-0.28-0.62	-0.019	*0.934*	-0.46-0.42

Figure legend

Figure 1. Linear regression between Rasch-built fatigue severity scale (R-FSS) score and (a) distal compound muscle action potential (CMAP) amplitude, R^2=0.20, correlation coefficient -0.52 (*p=0.007*), (b) distal CMAP area, R^2=0.36, correlation coefficient -0.55 (*p=0.003*), (c) proximal CMAP amplitude, R^2=0.26, correlation coefficient -0.482 (*p=0.013*), (d) proximal CMAP area, R^2=0.34, correlation coefficient -0.52 (*p=0.006*). Graph shows best-fit line and 95% confidence band of best-fit line.