Electrophysiological analysis of fatigue in neuromuscular disease

（神経筋疾患における疲労の電気生理学的解析）

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Abstracts

Background and purpose : Fatigue is an one of the major disabling problems in patients with neuromuscular disorders. Both nerve demyelination, and increased axonal branching associated with collateral sprouting reduce the safety factor for impulse transmission,.and could caused activity-dependent hyperpolarisation and conduction block during voluntary contraction, and thereby fatigue. This study aimed to investigate detailed nature of activity-dependent conduction block induced by voluntary contraction is associated with fatigue in demyelinating neuropathies and lower motor neuron disorders.

Methods: This study included 17 patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and 14 with spinal and bulbar muscular atrophy (SBMA). Sixteen healthy subjects served as controls. Fatigue was assessed with the fatigue scale for motor and cognitive functions (FSMC). Compound muscle action potential (CMAP) recording after median nerve stimulation and nerve excitability testing were performed before and after maximal voluntary contractions of the abductor pollicis brevis.

Results: CIDP and SBMA patients had prominent fatigue with higher FSMC motor scores ($P < 0.0001$) than controls. After voluntary contractions, CMAP amplitudes significantly decreased in 24% of CIDP and 7% of SBMA patients. The reduction of CMAP amplitudes was associated with the fatigue score on motor, but not on cognitive domains. After voluntary contraction, excitability testing showed axonal hyperpolarisation in the normal and CIDP/SBMA groups.

Conclusions: In patients with CIDP or SBMA, fatigue is caused by voluntary contraction-induced membrane hyperpolarization, when the safety factor is critically lowered due to demyelination or increased axonal branching, and this could be objectively assessed by CMAP amplitudes and excitability testing.

Introduction

Fatigue is one of the most common and troublesome symptoms in patients with neurological disorders [1], and a number of mechanisms are postulated. Major components of fatigue in neurological diseases are perceptions and performances [2]. Perceptions of fatigue have two aspects; homeostatic and psychological factors, whereas performance fatigability is composed of peripheral and central factors. Multiple mechanisms could be involved in single patients, and therefore it is difficult to evaluate fatigue.

The fatigue scale for motor and cognitive functions (FSMC) [3], which was invented to evaluate fatigue in multiple sclerosis, can separately assess cognitive and motor fatigue. Patients with neuropathy or anterior horn disease also experience prominent fatigue. Previous studies have suggested the contribution of activity-dependent hyperpolarization and conduction block in demyelinating neuropathies and lower motor neuron disorders. Several studies applied nerve excitability testing during voluntary contractions in chronic inflammatory demyelinating polyneuropathy (CIDP) [4] and multifocal motor neuropathy [5], and demonstrated that voluntary muscle contraction induces axonal membrane hyperpolarization, and when the safety factor for impulse transmission is critically reduced by demyelination, conduction block develops after muscle contractions.

Another study using stimulated-single fiber electromyography with high-frequency stimulation in spinal muscular atrophy and spinal bulbar muscular atrophy (SBMA) has shown motor nerve conduction block with gradual prolongation of latencies by axonal hyperpolarization [6]. Such conduction block is induced by the reduced safety factor presumably due to increased axonal branching associated with collateral sprouting; an action potential generated at one Ranvier node should depolarize multiple distal nodes to maintain saltatory conduction.

The aim of this study was to elucidate the relationship between nature of fatigue and activity-dependent hyperpolarization/conduction block in patients with neuromuscular disease. We enrolled CIDP and SBMA patients to validate the two mechanisms of the reduced safety factor, demyelination and increased axonal branching, respectively.

Methods

Subjects

A total of 31 patients with CIDP (n=17) or SBMA (n=14) were included in this study. All CIDP patients were diagnosed according to European Federation of Neurological Societies/ Peripheral Nerve Society (EFNS/ PNS) criteria [7]. All CIDP patients were in the partial remitting phase after immune treatment. SBMA patients were diagnosed by genetic testing, with an expanded CAG trinucleotide repeat in the first exon of the androgen receptor gene. Their motor function was assessed by overall neuropathy limitations scale (ONLS) [8], grip strength, medical research council (MRC) sum score [9], 9 hole peg test [10], and 6 minutes walk test [11]. MRC sum score (MRS-SS) was bilaterally evaluated in the following six muscles; shoulder abduction, elbow flexion, wrist extensor, hip flexion, knee extension, and ankle dorsiflexion muscles; ranges from 0 to 60. Control data were obtained from 16 healthy subjects. None of them had a neurological disorder, systematic disease, or medication affecting the peripheral nerve function.

All subjects provided written informed consent. Procedures of the present study were approved by the Ethics Committee of Chiba University School of Medicine.

Assessment of fatigue

Fatigability was assessed with fatigue scale for motor and cognitive functions (FSMC) [3]. The

FSMS questionnaire is composed of the two components; cognitive and motor domains. The 20 statements were related to patients' subjective perception of fatigue, cognitive and motor by halves; ten questions related to motor function like the need for more frequent or longer rests during physical activity, and ten questions focused on mental condition like the decrease of concentration under a stressful situation. Patients are asked to rate their level of agreement (toward 5) or disagreement (toward 0).

CMAP amplitude

Conventional motor and sensory nerve conduction studies (NCS) were performed in the median nerve. Compound muscle action potential (CMAP) was recorded from the abductor pollicis brevis (APB) muscle after stimulation at the wrist. After routine testing, CMAP amplitude was monitored after 1 minute maximal voluntary contractions (MVC). Maximal isometric voluntary abduction of the thumb against resistance, was provided by the same investigator (AT) for 1 minute. The cut-off value for the presence of activity-dependent conduction block was determined with the mean- 2 SD of normal control data.

Nerve excitability testing

Motor nerve excitability measurements were performed in the median nerve at the wrist, using a computerized program, the QTRAC software (copyright, Institute of Neurology, University College London, London, distributed by Digitimer Ltd) [12]. Stimulus current was applied using an isolated linear bipolar constant current stimulator (DS5, Digitimer Ltd). Stimulations were made with non-polarizable electrodes, placed surface electrodes 3 cm apart at the wrist, and an anode electrode placed 10 cm proximal to the stimulation electrode, not over the nerve. A ground electrode was placed at the palm. Compound muscle action potentials (CMAP) were

recorded in the APB muscle with the active electrode at the motor point, and a reference placed 4 cm distally.

We used the "multitrack" protocol to continuously monitor and record real-time excitability of motor axons in the median nerve at the wrist, as previously described [13 14 15] . The nerve excitability parameters were comprised of 5 measurements tracked by different five channels as follows: channels 1 and 6 were used to track the steepest portion of the stimulus–response curve of CMAPs, using long (1.0 ms) (channel 1) and short (0.1ms) (channel 6) duration stimuli to calculate strength-duration time constant (SDTC). Channels 2 and 3 monitored a stimulus following a conditioning stimulus of 100 ms of 40% of threshold depolarizing current pulse (channel 2) and a conditioning stimulus of 100ms of 40% of threshold hyperpolarizing current pulse (channel 3), respectively. Channel 5 monitored superexcitability, using a test stimulus delivered 6.3ms after a supramaximal conditioning stimulus.

Subjects were taken 20 minutes of monitoring and recording real-time excitability. During the test, they were performed 1 minute' isometric maximal voluntary abduction of the thumb in the same way as NCS testing. Before applying MVC, a stable baseline recording was established for at least 4 minutes, and stimuli were stopped during the voluntary contraction.

Statistical analyses

All statistical analyses were performed using JMP version 15 software. In analyses of clinical profiles, electrophysiological study parameters, and excitability properties, Student's t-test for unrelated samples, Fisher's exact test, or Dunnett's multiple comparison test was used to comparing normal and disease cohorts. Data are given as mean (SEM). Differences were considered significant at p-values < 0.05.

Results

Clinical profiles and motor function in normal controls and patients with CIDP or SBMA are shown in **Table1**. The mean age was higher in SBMA patients than normal control ($P < 0.05$), and all SBMA patients were male. Motor function was impaired in the patient groups; grip strength in CIDP ($p< 0.01$) and SBMA ($p< 0.0001$), 9 hole peg time in CIDP ($p <0.05$) and SBMA ($p<0.01$), distances in 6 minutes walk test in CIDP ($p <0.01$) and SBMA ($p <0.0001$), compared with normal controls.

Fatigue score

Results of fatigue scale (FSMC) are shown in **Figure 1.** The motor score of FSMC was significantly higher in CIDP ($p < 0.01$) and SBMA ($p < 0.01$) than in normal control. In contrast, there were no differences in the cognitive score of FSMC among the normal, CIDP, and SBMA groups. These results indicated that the patients with CIDP and SBMA have prominent fatigue of performance, whereas cognitive component does not significantly contribute to their fatigue.

CMAP amplitude and activity-dependent conduction block

Results of median motor nerve conduction studies are shown in **Table 2**. Baseline CMAP amplitudes were smaller for CIDP and SBMA patients, compared with normal controls. After 1 minute MVC, the mean CMAP amplitude decrease was significantly greater in the CIDP group, whereas the mean value was similar in the normal and SBMA group. **Figure 2A** shows changes in CMAP amplitude in individual subjects. When the cut-off value for abnormal CMAP reduction was defined as the normal mean - 2SD (93%), activity-dependent conduction block was present in 4 (24%) of the 17 CIDP and 1 (7%) of the 14 SBMA patients. Representative

CMAP waveforms in a single patient with CIDP are shown in **Figure 2B**.

CIDP Patients with activity-dependent conduction block had significantly higher FSMC motor scores than those without it. In the SBMA group, a single patient with activity-dependent conduction blocks showed high FSMC motor score (**Figure 3**).

Nerve excitability testing

Baseline data of nerve excitability testing are presented in **supplementary-table1**. Briefly, excitability properties in CIDP were characterized by greater threshold changes in threshold electrotonus, presumably due to decreased myelin resistance by demyelination [16]. SBMA patients showed longer SDTC, suggesting increased persistent nodal sodium currents, possibly because of collateral sprouting [17], consistent with previous reports

Changes in excitability indices after voluntary contraction are shown in **supplementary-table 2** and **Figure 4**. In all normal, CIDP, and SBMA groups, major changes were similar; increased threshold current, shortened SDTC, fanning-out in threshold electrotonus, and increased superexcitability, all of which indicated that axons were hyperpolarized after voluntary contraction [18] .

Discussion

Our results confirmed that patients with neuromuscular disease suffer prominent fatigue, and showed that some patients actually develop activity-dependent conduction block by voluntary contraction-induced axonal hyperpolarization, and the presence of conduction block was associated with more severe fatiguability. Moreover, our findings also showed that using threshold tracking, axonal membrane is hyperpolarized during voluntary contraction.

We hypothesized that there are two mechanisms of the reduced safety factor for impulse

transmission; demyelination and increased axonal branching, and therefore included patients with representative demyelinating neuropathy, CIDP, and those with chronic denervation and re-innervation by collateral sprouting, SBMA. Whatever the mechanisms of decreased safety factor, slight axonal hyperpolarization induces conduction block, and thereby muscle fatigue. It is reported that during maximal voluntary contraction, high-frequency impulse transmission (usually up to 30 Hz) activates electrogenic Na^+/K^+ pump. This pump exchanges three Na^+ ions for two K^+ ions, yield a net positive electrogenic charge and result in axonal hyperpolarization. This physiological process in daily activity can cause activity-dependent conduction block, if the safety factor is reduced by pathology.

The present study firstly applied FSMC for CIDP and SBMA patients and discovered fatiguability results from physical (peripheral motor) rather than cognitive factors. The term "fatigue" is used in many meanings. FSMC has been developed to separately evaluate physical and cognitive aspects of fatigue in multiple sclerosis [3] and recently applied for other neurological diseases [19]. Items in FSMC for motor subscale are composed of assessments mainly for skillfulness, stamina, muscle strength, speed and physical energy. It is not surprising that CIDP and SBMA patients have non-cognitive fatigue.

There are several limitations in this study. First, included CIDP patients were already treated, and in the remitting phase. This led to failure to evaluate maximal fatigue in these patients. Secondly, CMAP was recorded from APB, which might underestimate fatigue in SBMA patients with proximal muscle weakness. Finally, our threshold tracking study showed threshold increase of 12 to 18% after voluntary contraction (supplementary-table 2). The slight hyperpolarization would induce conduction block in the limited subgroup of patients.

Findings of the present study suggest that in neuromuscular disorders, fatigue is caused by different pathology, including at least two; nerve demyelination and increased axonal branching.

However, irrespective of the mechanisms, the fact that slight axonal axonal hyperpolarization by physiological activity leads to fatigue, could provide anew insight into symptomatic treatments. Digitalis, an inhibitor of electrogenic Na^+/K^+ pump, may reduce the extent of membrane hyperpolarization. Separately serum potassium levels largely affect resting membrane potential, and therefore some diet could alter membrane potential. Modulation of axonal membrane potential could be a treatment option for severe muscle fatigue. We would like to do such trial in the near future.

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Figure

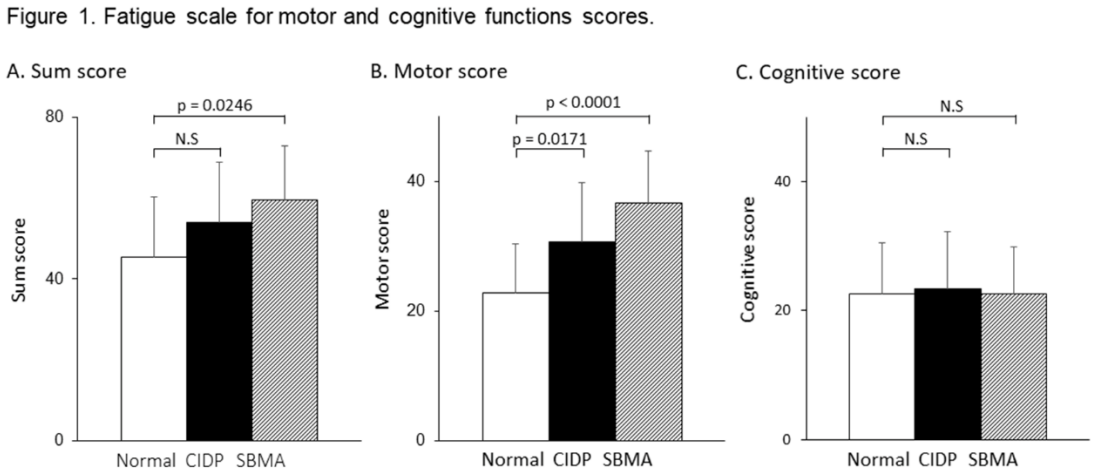

Figure 1. Fatigue scale for motor and cognitive functions scores.

The score of Fatigue Scale for Motor and Cognitive Functions (FSMC) in 17 chronic inflammatory demyelinating polyneuropathy (CIDP) and 14 spinal and bulbar muscular atrophy (SBMA) patients were compared with those of 16 normal control (NC). The sum score of the motor part was higher in CIDP ($P < 0.05$) and in SBMA ($P < 0.0001$) compared with NC. Whereas the score of the cognitive function was almost the same as normal controls.

Data are presented as mean, and error bars indicate SEM. N.S., not significant.

Figure 2. A. Changes in neurophysiological parameters following maximal voluntary contraction. B. The representative superimposed compound muscle action potential recordings before and after maximal voluntary contractions.

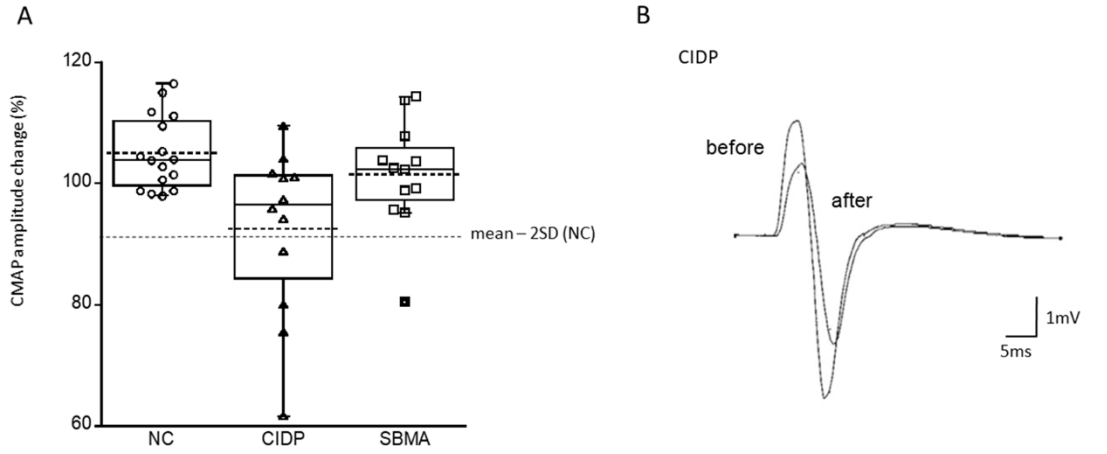

Figure 2. A. Changes in neurophysiological parameters following maximal voluntary contraction. B. The representative superimposed compound muscle action potential recordings before and after maximal voluntary contractions.

A. Amplitudes changes in compound muscle action potential (CMAP) of abductor pollicis brevis (APB), after 1 minute's voluntary contraction in normal control (NC), chronic inflammatory demyelinating polyneuropathy (CIDP), and spinal and bulbar muscular atrophy (SBMA). The cut-off value of 93% (dotted line) was determined as the mean – 2 standard deviation based on the normal control data.

B. The representative compound muscle action potential (CMAP) recordings from the abductor pollicis brevis with stimulation sites at the wrist in a chronic inflammatory demyelinating polyneuropathy (CIDP) subject. The superimposed two waveforms were recorded before and after 1 minute's maximal voluntary contraction to ensure the presence of activity-dependent conduction block by decreased CMAP amplitudes.

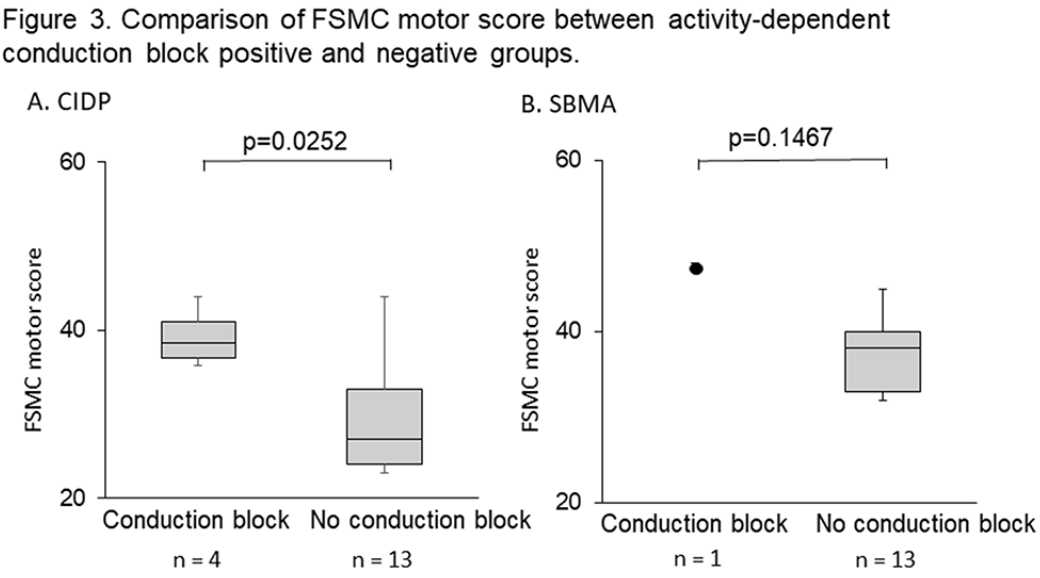

Figure 3. Comparison of FSMC motor score between activity-dependent conduction block positive and negative groups.

The motor score of The Fatigue Scale for Motor and Cognitive Functions (FSMC) of activity-dependent conduction block (ADCB) positive and negative groups in chronic inflammatory demyelinating polyneuropathy (CIDP) and spinal and bulbar muscular atrophy (SBMA) patients. The box plot shows the median and IQR of the third and first quartiles. The notches on the box plots indicate the maximum and minimum data. In both CIDP and SBMA categories, the ADCB positive groups felt more significant fatigue than the ADCB opposing groups (CIDP; P =0.0252).

Figure 4. Changes in excitability parameters following maximal voluntary contraction in each group.

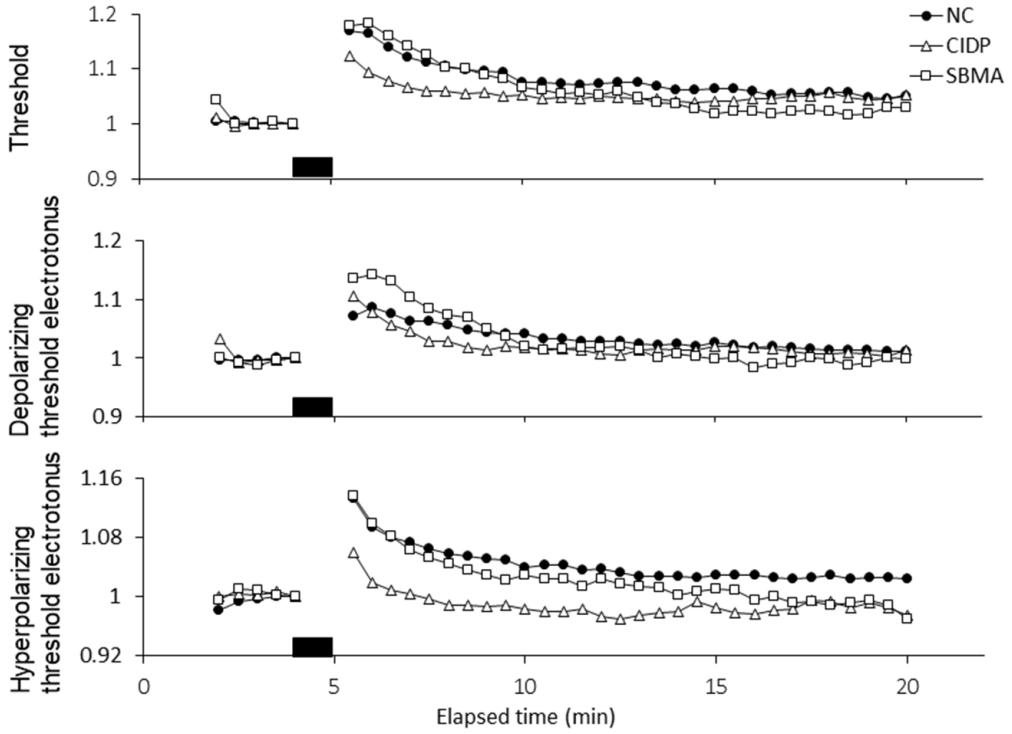

Figure 4. Changes in excitability parameters following maximal voluntary contraction in each group.

Comparison of changes in excitability parameters recorded from the median nerve before, during, and after maximal voluntary contraction of abductor pollicis brevis for 1 minute. The black horizontal bar indicates a period of maximal voluntary contraction. Each trace represents the mean data for 12 normal controls (filled circles), 17 CIDP patients (open triangles), and 14 SBMA patients (open squares). Data have been averaged over consecutive 30seconds intervals. All data were normalized to the precontraction. (A) Threshold current using test stimuli of 1.0 ms duration. (B) (C) Threshold electrotonus (TE) disclosed greater threshold changes in both depolarizing and hyperpolarizing in NC and SBMA. These findings suggest the hyperpolarizing changes after maximal voluntary contraction. The changes were more significant in NC and SBMA than CIDP.

Table1. Clinical profiles			
	Normal	CIDP	SBMA
	(n=16)	(n=17)	(n=14)
Age (years)	48 (2.7)	56 (4.7)	61 (2.8) *
Gender (male: female)	11: 5	14: 3	14: 0 *
Disease duration (months)	N.A.	33 (5-105)	148 (116-192)
Motor function			
Grip strength (kg) (sum of both sides)	78 (5.6)	56 (6.3) **	33 (3.7) ***
9 hole peg (sec) (sum of both sides)	45 (2.3)	61 (5.5) *	62 (2.8) **
6 minutes walk (m)	602 (20)	409 (36) **	305 (37) ***
MRC sum score	60 (0)	58 (0.97)	52 (0.80) ***
Fatigue scale for motor and cognitive functions			
sum score	45 (3.7)	54 (3.6)	59 (3.7) *
motor score	23 (1.9)	31 (2.2) *	37 (2.1) ***
cognitive score	23 (2.0)	23 (2.1)	23 (2.0)
CIDP, chronic inflammatory demyelinating polyradiculoneuropathy;			
SBMA, spinal and bulbar muscular atrophy			
MRC sum score, medical research council sum score in the 12 muscles (0-60);			
N.A., not applicable			
Data are given as mean (SEM) or median (IQR).			
*p < 0.05, **p < 0.01, ***p < 0.0001; compared with normal.			

Table 2. Changes in CMAP amplitude and excitability indices following maximal voluntary contractions.		
	Normal (n=16)	CIDP (n=17)	SBMA (n=14)
Median nerve conduction study			
Distal latency (ms)	3.5 (0.09)	6.8 (0.57) ***	4.4 (0.26)
CMAP amplitude (mV)			
Before MVC	8.3 (0.54)	5.0 (0.83) **	5.1 (0.45) **
After MVC	8.7 (0.54)	4.6 (0.81) ***	5.2 (0.50) **
Ratio of post/pre MVC (%)	105 (1.5)	93 (4.0) **	101 (2.6)
Motor conduction velocity (m/s)	58 (0.71)	35 (13) ***	53 (2.6)
Excitability measurements			
Threshold	1.17 (0.024)	1.12 (0.027)	1.18 (0.038)
Strength-duration time constant	1.03 (0.023)	1.01 (0.037)	1.01 (0.022)
Depolarizing threshold electrotonus (100ms)	1.07 (0.011)	1.11 (0.017)	1.14 (0.028) *
Hyperpolarizing threshold electrotonus (100ms)	1.13 (0.024)	1.06 (0.012) *	1.14 (0.024)
Superexcitability	1.17 (0.076)	1.27 (0.16)	1.47 (0.20)
CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; SBMA, spinal and bulbar muscular atr		
CMAP, compound muscle action potential; MVC, maximal voluntary contraction		
Data are given as mean (SEM). *p < 0.05, **p < 0.01, ***p < 0.0001; compared with normal.		

Supplementary table 1. Excitability testing at baseline			
	Normal (n=16)	CIDP (n=17)	SBMA (n=14)
Excitability testing			
Strength-duration time constant (ms)	0.44 (0.02)	0.36 (0.015) *	0.51 (0.028) *
Depolarizing threshold electrotonus (100ms; %)	45.9 (0.78)	52.7 (1.79) **	51.4 (1.89) *
Hyperpolarizing threshold electrotonus (100ms; %)	-125 (4.6)	-144 (7.0) *	-130 (4.8)
Superexcitability (%)	-8.74 (0.93)	-8.61 (1.22)	-12.9 (1.58) *
CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; SBMA, spinal and bulbar muscular atrophy			
CMAP, compound muscle action potential; MVC, maximal voluntary contraction			
Data are given as mean (SEM). *p < 0.05, **p < 0.01, ***p < 0.0001; compared with normal.			

Supplementary table 2. Changes in excitability indices following maximal voluntary contractions.			
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