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Prominent fatigue in spinal muscular atrophy and spinal and bulbar muscular atrophy: Evidence of activity-dependent conduction block

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HIGHLIGHTS

- We showed that patients with chronic lower motor neuron disease [spinal muscular atrophy and spinal and bulbar muscular atrophy (SMA/SBMA)] frequently suffer disabling muscle fatigue.
- Single fiber electromyography with high-frequency stimulation revealed that SMA/SBMA patients might have activity-dependent conduction block phenomenon in distal motor axons.
- Activity-dependent conduction block is presumably produced by the reduced safety factor due to markedly increased axonal branching associated with collateral sprouting.

ABSTRACT

Objectives: To clarify whether patients with spinal muscular atrophy (SMA) or spinal and bulbar muscular atrophy (SBMA) suffer disabling muscle fatigue, and whether activity-dependent conduction block (ADCB) contributes to their fatigue. ADCB is usually caused by reduced safety factor for impulse transmission in demyelinating diseases, whereas markedly increased axonal branching associated with collateral sprouting may reduce the safety factor in chronic lower motor neuron disorders.
Methods: We assessed the fatigue severity scale (FSS) in 22 patients with SMA/SBMA, and in 100 disease controls (multiple sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy (CIDP), and axonal neuropathy). We then performed stimulated-single fibre electromyography (s-SFEMG) in the extensor digitorum communis (EDC) muscle of 21 SMA/SBMA patients, 6 CIDP patients, and 10 normal subjects.
Results: The FSS score was the highest in SMA/SBMA patients [4.9 ± 1.1 (mean ± SD)], with 81% of them complaining of disabling fatigue, compared with normal controls (3.5 ± 1.0), whereas patients with multiple sclerosis (4.3 ± 1.6), myasthenia gravis (4.0 ± 1.6) or CIDP (4.3 ± 1.4) also showed higher FSS score. When 2000 stimuli were delivered at 20 Hz in s-SFEMG, conduction block of single motor axons developed in 46% of patients with SMA/SBMA, and 40% of CIDP patients, but in none of the normal controls.
Conclusion: SMA/SBMA patients frequently suffer from disabling fatigue presumably caused by ADCB induced by voluntary activity.
Significance: ADCB could be the mechanism for muscle fatigue in chronic lower motor neuron diseases.

1. Introduction

Fatigue and weakness are common complaints of neurological disorder patients and significantly impair the quality of life. It is

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widely known that fatigue is one of the most disabling symptoms in patients with multiple sclerosis (MS) (Krupp et al., 1988) and those with chronic inflammatory demyelinating polyneuropathy (CIDP) (Boukhris et al., 2005; Bissay et al., 2008). Activity-induced fatigue and weakness were also described in not only patients with MS and CIDP but also with multifocal motor neuropathy (Cappelen-Smith et al., 2000; Kaji et al., 2000; Vucic et al., 2010; Straver et al., 2011).

In addition to demyelinating diseases, patients with a neurodegenerative motor neuron disorder often complain of fatigability. Persistent fatigue is a common complaint in patients with amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) (Piepers et al., 2008; McElhiney et al., 2009), and is associated with an impaired quality of life (Robbins et al., 2001). Straver et al. demonstrated that SMA patients had activity-induced weakness more often than normal subjects (Straver et al., 2011). Spinal and bulbar muscular atrophy (SBMA) is also a slowly progressive lower motor neuron disease, and SBMA patients may therefore show fatigability.

Activity-induced fatigue and weakness are caused by repetitive activity or exertion. It has been suggested that this phenomenon is attributable to activity-dependent conduction block (ADCB) arising in demyelinated axons. After repetitive firing, ionic concentration gradients in the axon are restored by increased Na^+/K^+ pump activity (Bostock and Grafe, 1985). Thus, with each pump-cycle, three Na^+ ions are expelled and only two K^+ ions enter (i.e., electrogenic pump), and the axons hyperpolarized by the pump (Schoepfle and Katholi, 1973), resulting in a decrease in the safety factor for impulse transmission. Nerve conduction is blocked if the safety factor is below unity due to leakage of the driving current caused by demyelination. In lower motor neuron disorders, the safety factor could also be reduced at the distal branching points due to collateral sprouting. Therefore, it is possible that ADCB could occur and may contribute to fatigue and weakness in SMA and SBMA patients.

We have developed a novel method to assess axonal activity-dependent hyperpolarization at a constant stimulus frequency using intra-muscular axonal stimulated-single fiber electromyography (s-SFEMG) (Noto et al., 2011). It was shown that tetanic stimulation at a constant rate (5, 10, and 20 Hz) resulted in a significant latency increase in single human motor axons, the extent of which depended on the stimulus frequency. This technique may detect ADCB if the safety factor is significantly reduced by demyelination or increased branching.

Given the recent interest in the mechanism of fatigue and weakness in demyelinating or chronic neurogenic diseases, the aim of this study was to assess the severity of fatigue in patients with SMA or SBMA, and to investigate whether ADCB contributes to fatigue in such patients.

2. Patients and methods

The study was conducted at Chiba University Hospital between October 2009 and March 2011. Informed consent was provided by each subject, and all experiments and the study protocol were conducted in accordance with the Declaration of Helsinki and with the approval of the Ethics Committee of Chiba University School of Medicine for Human Research Studies.

2.1. Subject

The present study included five different patient groups [SMA/SBMA, CIDP, MS, myasthenia gravis (MG), and axonal neuropathy] and normal subjects. The SMA/SBMA group ($n = 22$) consisted of 5 SMA patients and 17 SBMA patients; one of the 5 SMA patients had mutation of the SMN gene and the remaining SMA patients did not have genetic testing and were diagnosed based on the clinical/familial history and electrophysiological examination. All SBMA patients had expanded CAG repeats of the androgen receptor. Disease durations of SMA and SBMA patients were 22.6 ± 9.5 (mean ± SD) years and 10.2 ± 6.4 years, respectively. Modified Rankin Scale scores were 3.2 ± 0.8 and 2.2 ± 0.4.

The CIDP ($n = 16$), MS ($n = 31$), and MG ($n = 33$) groups consisted of consecutive patients in the study period. Neuropathy patients ($n = 20$) consisted of 13 patients with diabetic polyneuropathy, 6 with vasculitic neuropathy and 1 with vitamin B12 deficiency. This study also included 58 normal healthy subjects; none of whom had a neurological disorder, systematic disease, or was taking medication affecting the peripheral nerve function.

s-SFEMG was performed in 21 SMA/SBMA patients, 6 CIDP patients, and 10 normal subjects who consented to the examination protocol.

2.2. Assessment of fatigue

Fatigue was assessed by the Fatigue Severity Scale (FSS) (Krupp et al., 1989). The FSS was developed as a method of evaluating fatigue in patients with MS and other conditions such as systemic lupus erythematosus. The FSS questionnaire is composed of the following 9 statements related to patients' subjective perception of fatigue and its consequences for everyday activities: 1. My motivation is lower when I am fatigued, 2. Exercise brings on my fatigue, 3. I am easily fatigued, 4. Fatigue interferes with my physical functioning, 5. Fatigue causes frequent problems for me, 6. My fatigue prevents sustained physical functioning, 7. Fatigue interferes with carrying out certain duties and responsibilities, 8. Fatigue is among my three most disabling symptoms, 9. Fatigue interferes with my work, family, or social life. Patients are asked to rate their level of agreement (toward 7) or disagreement (toward 0) with the 9 statements. The final score represents the mean value of the 9 items.

2.3. Stimulated-single fiber electromyography

s-SFEMG was performed in the extensor digitorum communis muscle (EDC) using a Nicolet Viking 4 EMG machine (Nicolet Biomedical Japan, Tokyo, Japan), as described previously (Noto et al., 2011). The recordings were made intra-muscularly with a concentric needle electrode (30 G; TECA elite US53153). The high pass filter was set to 2 kHz and the low pass filter to 10 kHz. Intramuscular axonal stimulation was performed with a monopolar needle electrode (28 G; TECA U0809P02) and a reference surface electrode placed 2 cm laterally (Fig. 1). The stimulus duration was 0.1 ms. The distance between the stimulating and recording electrodes was 2 cm. The stimulus intensity was initially determined as 20% above the activation threshold of the target muscle action potential (MAP).

Before this study was performed, we predicted that blockings might occur due to slight movement of either the stimulating or recording electrodes produced by the muscle twitch. To avoid this phenomenon, the fingers of subjects and electrodes were fixed with a strap or a strut as shown in Fig. 1. In fact, during 20-Hz stimulation, the muscle twitch of the EDC muscle was not observed because 20-Hz axonal-stimulation produced persistent contraction of muscle bundles in all subjects. Therefore, the probability of blockings due to the movement of electrodes was low. We also observed the return of a previously blocked muscle action potential after rest in some recordings with blocking. However, we had to wait for over 15 min in each site in order to clear the effect of axonal hyperpolarization (Kiernan et al., 2004), and long time waiting