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Impaired post-tetanic potentiation of muscle twitch in myasthenia gravis

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HIGHLIGHTS

- A novel method using an accelerometer was used to evaluate post-tetanic potentiation of muscle twitch in myasthenia gravis.
- Significant decrease in post-tetanic potentiation of muscle twitch may be associated with impairment of excitation–contraction coupling in myasthenia gravis.
- The present method has high sensitivity in detecting impairment of excitation–contraction coupling in myasthenia gravis.

ABSTRACT

Objective: The aim of this study was to evaluate post-tetanic potentiation of muscle twitch in myasthenia gravis (MG).
Methods: Post-tetanic potentiation was evaluated by recording the compound muscle action potential (CMAP) of abductor pollicis brevis and movement-related potential (MRP) of the thumb using an accelerometer after tetanic stimulation of the median nerve at the wrist. After baseline recording, tetanic stimulation was delivered to the median nerve at a frequency of 10 Hz for 10 s. The CMAP and MRP were successively recorded at baseline and at 5, 10, 30, 60, 90 and 120 s after tetanic stimulation. The chronological changes of CMAPs and MRPs were recorded bilaterally in 11 patients with MG, 9 patients with myopathies (disease controls), and 25 healthy control subjects.
Results: Maximal acceleration of MRP was significantly elevated during 10 s after tetanic stimulation without any CMAP changes in all groups. However, statistical analysis detected a significant decrease in post-tetanic potentiation of maximal acceleration of MRP in MG patients only compared to healthy controls, but not in myopathy patients, which may imply impairment of excitation–contraction coupling in MG.
Conclusions: Post-tetanic potentiation of muscle twitch is significantly diminished in MG, suggesting impaired excitation–contraction coupling.
Significance: Measurement of post-tetanic potentiation using an accelerometer is a simple and sensitive method to detect impairment of excitation–contraction coupling in MG.

1. Introduction

Although defective neuromuscular transmission is known to be a cause of muscle weakness in myasthenia gravis (MG), previous studies have shown the possible roles of other processes, the failure of which may also cause muscle weakness in MG. Especially,

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excitation–contraction coupling may be defective in patients with MG (Pagala et al., 1990, 1993; Slomić et al., 1968). The excitation–contraction coupling in skeletal muscle is the process whereby an action potential triggers a muscle fiber to contract. Some investigators have applied the post-tetanic potentiation and/or the staircase phenomenon to elucidate the impairment of excitation–contraction coupling in MG (Krarup, 1977; Slomić et al., 1968). Post-tetanic potentiation is the enhancement of active twitch force following high-frequency tetanic stimulation (Brown and von Euler, 1938), while the staircase phenomenon is the progressive increase in active twitch force during repetitive low-frequency stimulation (Bowditch, 1870/71). The post-tetanic potentiation and staircase phenomenon have been explained by an increase in sarcoplasmic Ca^{2+}, which may induce facilitation of excitation–contraction coupling after tetanic stimulation and stepwise increase in response during repetitive twitch, respectively. Studies in MG patients have demonstrated a correlation between the magnitude of potentiation and the severity of MG, and proposed the significance of impaired excitation–contraction coupling in MG (Krarup, 1977; Slomić et al., 1968). However, post-tetanic potentiation and staircase phenomenon are rarely used to evaluate the impairment of excitation–contraction coupling in the clinical laboratory, presumably because complicated apparatus using a strain gauge is required.

In this study, we describe a novel procedure to measure post-tetanic potentiation using an accelerometer attached to the hand muscle instead of the complicated apparatus with a strain gauge used in previous studies. Our method is simple and may be a useful clinical test for the detection of impairment of excitation–contraction coupling in MG.

2. Materials and methods

2.1. Subjects and protocol

We studied 11 patients with MG (3 males and 8 females; aged 33–67 years, mean 47.2 years) at Sapporo Medical University Hospital. The diagnosis of MG was based on typical clinical features and electrophysiological evidence of a defect in neuromuscular transmission, which is either an abnormal decrement in repetitive nerve stimulation tests (muscles tested: orbicularis oculi, nasalis, trapezius, abductor pollicis brevis and abductor digiti minimi), or increased jitter on concentric needle single fiber electromyography of the voluntarily activated extensor digitorum communis and orbicularis oculi muscles (Kokubun et al., 2012; Kouyoumdjian and Stålberg, 2008). Acetylcholine receptor (AChR) binding antibody was measured in a commercial laboratory using a radioimmunoassay. In MG patients without AChR antibody, serum antibody against muscle-specific receptor tyrosine kinase (MuSK) was measured by immunoprecipitation of ^{125}I-recombinant MuSK extracellular domains (Shiraishi et al., 2005). The diagnosis of thymic lesion was based on histopathological findings after extended thymectomy.

At the time of the present study, 1 of 11 patients had never received any specific MG therapy, and the remaining 10 patients showed exacerbation of myasthenic symptoms despite receiving corticosteroids alone (5 patients), or corticosteroids combined with tacrolimus (4 patients) or cyclosporine (1 patient). Extended thymectomy had already been performed in 8 patients. Disease severity was graded according to the clinical classification of Myasthenia Gravis Foundation of America (MGFA) (Jaretzki et al., 2000).

We also studied 25 healthy control subjects (9 males and 16 females) aged 26–60 years (mean, 40.2 years) to establish the normal ranges for the methods used in this study, and 9 patients with myopathies (3 males and 6 females) aged 21–66 years (mean, 48.4 years) to examine whether myopathic changes influence excitation–contraction coupling (Table 1). Myopathies included autoimmune myositis, muscular dystrophy and muscle sarcoidosis.

All the healthy control subjects and patients gave informed consent for participation in this study. The study was approved by the Ethics Committee, Sapporo Medical University Hospital, Sapporo, Japan.

Table 1
Comparison of age, grip power and electrophysiological findings in subject groups.

		Subject group			*F* value
		Healthy control	Myasthenia gravis	Myopathy	
Number of subjects (males, females)		25 (9, 16)	11 (2, 9)	9 (3, 6)	
Age (years)		40.2 (11.3, 27–60)	47.2 (12.8, 33–67)	48.4 (14.0, 21–66)	
Number of hands tested		50	22	18	
Grip power (kg)	Lt + Rt	32.4 (8.5, 21–54)	19.2 (10.3, 5–48)**	16.4 (8.8, 3.5–35)**	0.09
	Lt	31.0 (7.5, 21–46)	18.9 (9.6, 10–43)**	15.4 (9.4, 3.5–32)**	0.25
	Rt	33.7 (9.4, 23–54)	19.5 (11.3, 5–48)**	17.4 (8.7, 5–35)**	0.38
CMAP amplitude (mV)	Lt + Rt	10.6 (1.9, 6.9–13.8)	8.0 (2.7, 3.5–14.3)**	9.1 (3.4, 1.5–15.1)	4.60
	Lt	11.0 (1.7, 7.0–13.5)	7.9 (2.5, 4.1–11.2)**	9.3 (3.3, 3.1–13.3)	3.00
	Rt	10.3 (2.0, 6.9–13.8)	8.2 (3.0, 3.5–14.3)	8.8 (3.8, 1.5–15.1)	2.16
CMAP area (msmV)	Lt + Rt	30.0 (5.7, 17.7–42.6)	22.2 (7.9, 10.2–39.8)**	25.9 (10.5, 4.0–42.4)	5.12
	Lt	30.5 (5.2, 22.5–42.6)	22.9 (9.1, 10.3–39.8)*	26.5 (11.0, 6.8–42.4)	4.67
	Rt	29.4 (6.2, 17.7–42.1)	21.5 (7.0, 10.2–35.3)**	25.3 (10.7, 4.0–40.2)	1.32
Maximal acceleration at baseline (m/s^2)	Lt + Rt	5.5 (3.8, 1.6–17.6)	2.9 (1.0, 0.8–5.3)**	3.2 (1.6, 0.6–7.4)*	8.64
	Lt	5.6 (4.0, 1.8–17.6)	2.9 (0.9, 1.6–4.0)**	3.2 (1.4, 0.6–5.1)	3.26
	Rt	5.4 (3.6, 1.6–14.7)	2.8 (1.2, 0.8–5.3)	3.2 (1.8, 1.2–7.4)	6.06
Maximal acceleration at 5 s after TS (m/s^2)	Lt + Rt	9.5 (7.2, 2.7–36.0)	4.2 (1.7, 1.1–8.1)**	5.3 (2.7, 1.0–10.3)*	8.99
	Lt	9.9 (7.9, 3.1–36.0)	4.3 (1.6, 2.1–6.5)**	5.4 (2.9, 1.0–9.5)	3.57
	Rt	9.0 (6.6, 2.7–28.1)	4.0 (1.8, 1.1–8.1)*	5.2 (2.7, 1.7–10.3)	6.17
PTP of MRP acceleration (5 s after TS divided by baseline)	Lt + Rt	1.7 (0.4, 1.0–2.6)	1.5 (0.2, 1.0–2.0)**	1.7 (0.4, 1.0–2.2)	1.56
	Lt	1.8 (0.4, 1.2–2.6)	1.4 (0.2, 1.2–1.9)	1.7 (0.4, 1.0–2.2)	1.97
	Rt	1.7 (0.3, 1.0–2.2)	1.5 (0.3, 1.0–2.0)	1.6 (0.3, 1.1–2.1)	0.16

Data are expressed as mean (SD, range) for age, grip power, CMAP amplitude, CMAP area, ECCT, and acceleration parameters. Single asterisk and double asterisks denote $p < 0.05$ and $p < 0.01$, respectively, compared to healthy control values, as analyzed by Mann–Whitney *U*-test. CMAP, compound muscle action potential; MRP, movement-related potential; ECCT, excitation–contraction coupling time; TS, tetanic stimulation; PTP, post-tetanic potentiation, Lt, left hand; Rt, right hand.