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Opinion paper

Palpebral portion of the orbicularis oculi muscle to repetitive nerve stimulation testing: A potential assessment indicator in patients with generalized myasthenia gravis

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ABSTRACT

Repetitive nerve stimulation (RNS) is a valuable diagnostic method for myasthenia gravis (MG). However, its association with clinical severity was scarcely studied. We reviewed medical records and retrospectively enrolled 121 generalized MG patients. Sensitivity of different muscles to RNS and clinical scoring systems was evaluated. RNS testing revealed facial muscles have the highest positive rate, followed by proximal muscles and distal muscles, with the palpebral portion of the orbicularis oculi muscle most sensitive. Amplitude decrement of compound muscle action potential (CMAP) in the palpebral portion of the orbicularis oculi muscle is related to quantitative myasthenia gravis (QMG) scores, MG-specific manual muscle testing (MMT) scores and myasthenia gravis-related activities of daily living (MG-ADL) scores. We suggest that RNS testing of the palpebral portion of the orbicularis oculi muscle is a potential assessment indicator in patients with generalized MG.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease manifested by impairment at the neuromuscular junction (NMJ) featured by weakness and fatigability [1]. MG is a T cell-mediated disorder with autoantibodies targeting acetylcholine receptor (AChR), muscle-specific kinase (MuSK), lipoprotein-related protein 4 (LRP4), agrin, or other potentially related proteins at the NMJ [1,2]. MG patients present with variable symptoms, including fluctuating ptosis, diplopia, dysarthria, dysphagia, dyspnea, facial weakness, and generalized fatigue. Although there are different subgroup classifications of MG [3,4], patients are normally divided into ocular MG (OMG), generalized MG (GMG), and MG crisis according to clinical presentation. Ocular muscles are reported to be the most frequently involved skeletal muscle in clinical evaluation, damaged in about 85% of patients [5,6] and in approximately 75% of generalized MG patients [7].

The diagnosis of MG mainly relies on clinical manifestation, antibody detection, acetylcholinesterase inhibitor testing, and electrophysiological examination [4]. Repetitive nerve stimulation (RNS) is now regarded as a routine electrophysiological test and plays an important role in the diagnostic criteria and differential diagnosis [4,8]. In the contrast, there is a paucity of reports outlining the interrelation between RNS and clinical scales. A previous study discussed the theoretical association between RNS and clinical evaluation of disease severity [8]. Recently a study further explored the correlation between electrophysiological testing, including SFEMG and RNS in the frontalis, and clinical severities [9]. However, as the sensitivity of RNS is specific to unique muscle groups and different forms of MG [10,11], further detailed works concerning the relation between clinical scoring systems and electrophysiological markers are needed.

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Table 1
Sample characteristics.

121 Patients with generalized myasthenia gravis	
Age at onset (years)	44.4 (16.5)
Gender	
Females	74 (61.2%)
Males	47 (38.8%)
Disease duration (months)	7 (0–274)
MGFA classification	
Type I	0 (0.0%)
Type IIa	53 (43.8%)
Type IIb	45 (37.2%)
Type IIIa	13 (10.7%)
Type IIIb	9 (7.4%)
Type IVa	1 (0.9%)
Type IVb	0 (0.0%)
Type V	0 (0.0%)
Clinical presentation	
Ptosis	96 (79.3%)
Diplopia	69 (57.0%)
Weakness of eye closure	90 (74.4%)
Thymus scan	
Thymoma	32 (26.5%)
Thymic hyperplasia	19 (15.7%)
Negative scan	61 (50.4%)
Not examined	9 (7.4%)
RNS	
Positive*	121 (100.0%)
Negative	0 (0.0%)

* Positivity in at least 1 muscle is considered as RNS positive.

To date, the interrelation between electrophysiology and clinical severities in GMG patients is unclear. This study aims to find the most sensitive muscle to RNS and evaluate the correlation between compound muscle action potential (CMAP) amplitude decrement and clinical scoring systems in GMG patients, which may extend our understanding and utility of RNS.

2. Materials and methods

2.1. Patients

We reviewed medical records of all GMG patients diagnosed in the Department of Neurology, Huashan Hospital, Shanghai, China from 2013/08 to 2016/09 and retrospectively enrolled 121 candidates. These patients all underwent anti-AChR antibody test (enzyme-linked immunosorbent assay (ELISA) kits of RSR Limited, Pentwyn, Cardiff, United Kingdom), RNS, and clinical assessment (QMG score, MMT score, and MG-ADL score). The detailed inclusion criteria was: (1) clinical manifestation that is classified as the Myasthenia Gravis Foundation of America (MGFA) clinical classification Type II, III or IV; (2) anti-AChR antibody positivity; (3) patients that have not received pyridostigmine and/or immunosuppressive therapy at the initial electrophysiological testing.

The Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China approved the program, and informed consent was obtained from all study candidates.

2.2. RNS

The testing was performed using the Medtronic Keypoint.net EMG machine (Medtronic, Minneapolis, Minnesota). Superficial stimuli electrodes were placed in front of the ear. Recording electrodes were placed over the frontalis, palpebral and orbital portion of the orbicularis oculi muscle, nasalis, deltoid, trapezius and abductor pollicis brevis. Reference electrodes for facial muscles were placed at the contralateral side of stimuli electrodes, and those of limb muscles were placed over tendon insertion sites. A grounding electrode was put over the forehead. Facial stimulation pulse width was 0.1 ms and limb stimulation pulse width was 0.2 ms. Stimulus intensity was supramaximal (adding 30% intensity on the basis of the highest amplitude). We conducted 10 strain stimuli with a 3 Hz frequency, and compared the first and forth CMAP amplitude. A decrement of more than 10% was regarded as abnormal. We detected CMAP decrement of bilateral muscles and evaluated positive results for significance. In instances where bilateral results were both positive, we use the higher decrement value for analysis. The initial testing results of each individual were retrospectively collected.

2.3. Antibody detection

We measured serum antibodies against AChR using ELISA kits. The standard procedures for ELISA were performed following manufacturer's instruction (RSR Limited). The optical density was read at 450 nm within 30 min of adding stop solution. The result was presented as antibody titers. A titer of $\geq$0.45 nmol/L was defined as positive.

2.4. Clinical evaluation

Subjects we enrolled all had been assessed with the following clinical indicators of MG: the Myasthenia Gravis Foundation of America (MGFA) clinical classification [12], MGFA-recommended QMG scores [12], MG-specific MMT scores [13], and MG-ADL scores [14]. These assessments were administered by physicians and clinic coordinators in in the Department of Neurology, Huashan Hospital, Shanghai, China.

2.5. Statistical analysis

Continuous variables were described as means with standard deviation (SD), while categorical variables were presented as frequencies and percentages. Correlation between CMAP decrement and clinical scores were done using Pearson correlation tests. A P value of <.05 was considered statistically significant. Data were analyzed using GraphPad Prism 5.

3. Results

During the retrospective chart review study, a total of 121 GMG patients were eligible with a mean age of 44.4 years (SD = 16.5) and a female to male ratio of 74:47. Table 1 shows the main demographic and clinical data. Most patients were classified as MGFA Type IIa and Type IIb (Type II: mild weakness affecting other than ocular muscles with or without ocular muscle weakness of any severity; Type IIa: predominantly affecting limb, axial muscles or both; Type IIb: predominantly affecting oropharyngeal, respiratory muscles or both). Ptosis (79.3%), weakness of eye closure (79.3%) and diplopia (57.0%) are the three most common presentation. Thirty-two out of the 121 patients had thymoma. All the patients showed RNS positivity of at least 1 muscle (Table 1).

Among the 121 eligible candidates, 64 patients received RNS testing of all 7 muscles (see Materials and Method, RNS). The sensitivity of different muscles is shown in Fig. 1. Facial muscle had the highest positive rate (96.9%) when compared with proximal (84.0%) and distal muscles (51.6%). Only patient had a negative rate in facial muscle. With respect to single muscles, the muscles ranked by sensitivity to RNS from greatest to least are palpebral portion of the orbicularis oculi muscle (89.1%), deltoid (82.8%), orbital portion of the orbicularis oculi muscle (78.1%), nasalis (73.4%), trapezius (62.5%), frontalis (59.4%) and abductor pollicis brevis (51.6%) (Fig. 1).

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