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Clinical Study

Myopathic changes detected by quantitative electromyography in patients with MuSK and AChR positive myasthenia gravis

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ABSTRACT

Myopathic changes are frequent a electrophysiological finding in patients with muscle specific tyrosine kinase (MuSK) positive myasthenia gravis (MG). The aim of this study was to explore the importance of quantitative electromyography (EMG) in the detection of myopathic changes in MuSK MG patients. Classical and quantitative EMG were performed in 31 MuSK and 28 acetylcholine receptor (AChR) positive MG patients, matched by sex, age, disease duration and severity. Classical EMG revealed the presence of myopathic changes more frequently in MuSK MG compared to AChR MG patients, especially in the facial muscles. Quantitative EMG registered myopathic lesions more frequently than classical EMG, but the frequency was similar between MuSK and AChR MG patients. Quantitative EMG revealed myopathic changes in the majority of both MuSK and AChR positive MG patients. This examination is sensitive, but it cannot be used to differentiate between MG patients belonging to the different disease groups. It should not be used in isolation. Rather, it should complement classical EMG in the detection of myopathic changes.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease in which antibodies against targets on the postsynaptic muscle membrane cause neuromuscular transmission failure. About 85% of patients with MG have autoantibodies against acetylcholine receptor (AChR) [1]. In AChR negative MG patients antibodies to muscle specific tyrosine kinase (MuSK) have been identified in 40–50% of cases [2]. MG associated with anti-MuSK antibodies is considered to be a distinct clinical entity [3] and it differs in many aspects from the typical presentation of AChR positive MG (AChr MG). Unlike AChR MG patients, who experience weakness and fatigue in electrophysiologically normal muscles, myopathic changes have been described in patients with MuSK positive MG [4,5], as well as visible wasting of the tongue and facial muscles [3,6]. Moreover, MRI studies demonstrated fatty degeneration in the cranial muscles of MuSK positive MG (MuSK MG) patients, similar to patients with proven muscle disease such as myotonic dystrophy, while such changes were not present in patients with AChR MG [6]. Therefore, the muscle atrophy observed in the tongue and facial muscles of MuSK MG patients has been thought to be secondary to the myopathic process [7]. There is also evidence of significant muscle ultrastructural changes in MuSK MG patients. Myopathic and mitochondrial abnormalities are more prominent in MuSK MG with giant, swollen, and degenerated mitochondria with fragmented cristae. The most common changes in AChR MG muscles are fiber atrophy, myofibrillar disarray, and Z-line streaming, consistent with mild neurogenic abnormalities [8]. Since the origin of myopathic electromyography (EMG) changes in MuSK MG patients is still unclear, we aimed to further address this issue. Quantitative EMG methods, including turns/amplitude (T/A) and multi-motor unit potential (MUP) analysis, are more sensitive than regular EMG, which only qualitatively analyzes interference pattern and depends on subjective interpretation of the findings. The aim of this study was to explore the importance of quantitative EMG techniques in the detection of myopathic EMG changes in MuSK MG patients.

2. Methods

2.1. Patients

This is a prospective study of patients already diagnosed with MG. The study group consisted of 31 MuSK MG patients (25 women and six men) who were treated at the Neurology Clinic,

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Clinical Center of Serbia in Belgrade, Serbia. The control group consisted of 28 AChR MG patients (25 women and three men) with the generalized form of the disease, who were matched with MuSK MG patients by sex, age, disease duration and severity. The diagnosis of MG was established on the basis of a typical clinical presentation in the form of fluctuating weakness and fatigability of various skeletal muscles, positive decrement response of more than 10% on the repetitive nerve stimulation test or increased jitter on single fiber electromyography. Positive neostigmine or edrophonium tests were carried out to confirm the diagnosis. The disease severity was graded using the Myasthenia Gravis Foundation of America (MGFA) classification [9].

2.2. Clinical data

At the time of the study, MuSK MG patients were an average of 49.4 ± standard deviation (SD) 14.8 years old, ranging from 19–75 years, while the average age of AChR MG patients was 42.5 ± SD 15.8 years, with a range of 19–74 years. Mean disease duration of the MuSK MG group was 6.4 ± SD 6.8 years, with a range of 1–34 years, while it was 6.8 ± SD 5.6 years, varying from 0.1–20 years in AChR MG patients. Disease severity, at the time of the study, was also similar between the two groups. Five (16.1%) MuSK MG patients and three (10.7%) AChR MG patients were in remission. MGFA class IIA was registered in 10 (32.3%) MuSK MG and 11 (39.3%) AChR MG patients, class IIB was registered in 10 (32.3%) MuSK MG and 10 (35.7%) AChR MG patients, class IIIA in one (3.2%) MuSK MG and also in one (3.6%) AChR MG patient and class IIIB was registered in five (16.1%) MuSK MG and three (10.7%) AChR MG patients.

This study was approved by the Ethics Committee of the Medical Faculty of Belgrade University. All patients gave informed consent for participation in the study.

2.3. Antibody analysis

Anti-AChR antibody analysis was performed in sera of all patients by radioimmunoassay. The test was considered positive if the antibody titer was more than 0.2 nM. Anti-MuSK antibody titer was obtained in all AChR negative MG patients. The test was considered positive if the antibody titer was more than 0.02 nM.

2.4. EMG

EMG was performed by concentric needle electrode during relaxation and voluntary muscle activation on extensor digitorum communis (EDC), deltoid and orbicularis oculi (OO) muscles using a CareFusion Synergy EMG machine (CareFusion, San Diego, CA, USA). The EMG examiner was blinded to the patient's antibody status. The EMG finding was defined as normal or myopathic with short-duration, small-amplitude MUP.

Quantitative EMG analysis included T/A and multi-MUP analysis. T/A analysis was performed as the patient increased up to the maximal voluntary contraction of the EDC, deltoid and OO muscles. Multi-MUP analysis was performed during sustained mild voluntary muscle activation of deltoid and OO muscles. In every examined muscle, at least 20 MUP were collected and included in the analysis. Individual MUP durations were measured using an automatic cursor setting, which was manually adjusted when needed in order to mark the precise onset and termination of the MUP. Amplitudes and number of phases for each MUP were automatically measured.

2.5. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 15.0 (IBM, Armonk, NY, USA). The results of the study were statistically analyzed by means of the chi-square tests (or exact test), Student's *t*-test and Spearman rank correlation test, as appropriate. A p value of <0.05 was considered significant.

3. Results

In our previously published paper [10], EMG examination revealed the presence of myopathic EMG changes in around one-third of MuSK MG patients in the extremity muscles and in more than 80% in the facial muscles. Conversely, myopathic EMG changes were registered in around one-third of AChR MG patients in the facial muscles and were extremely rare in the extremity muscles.

T/A analysis was performed in the EDC, deltoid and OO muscles. In one AChR MG patient this examination could not be performed in the EDC and deltoid muscles due to severe weakness of these muscles. For the same reason, T/A analysis could not be performed in the OO muscle in two MuSK MG patients. The results of T/A analysis are presented in Table 1. T/A analysis registered similar results between MuSK MG and AChR MG patients. Number of MUP turns was the only registered parameter which was lower in the MuSK MG patients compared to the AChR MG patients (p = 0.043).

Multi-MUP analysis was performed in the deltoid and OO muscles and the results are presented in Table 2. Values of all analyzed MUP parameters were similar between MuSK and AChR MG patients (p > 0.05).

When the results of our MG patients were compared to the published reference values for MUP parameters in the OO [11] and deltoid [12] muscles, a myopathic lesion was confirmed in the OO muscle in 26 (83.9%) MuSK MG and 24 (85.7%) AChR MG patients,

Table 1
Results of T/A analysis in MuSK positive and AChR positive MG patients

T/A analysis	MuSK MG		AChR MG		Statistical significance
EDC	Range	Mean ± SD	Range	Mean ± SD	
MUP amplitude (μV)	155–946	378.2 ± 209.3	206–980	425.7 ± 178.4	p = 0.360
MUP number of turns	112–1193	515.2 ± 222.6	173–1050	629.1 ± 191.8	p = 0.043
Deltoid	Range	Mean ± SD	Range	Mean ± SD	
MUP amplitude (μV)	190–992	372.5 ± 213.8	191–1106	460.1 ± 292.9	p = 0.195
MUP number of turns	236–1108	547.6 ± 180.6	415–806	592.1 ± 98.0	p = 0.259
OO	Range	Mean ± SD	Range	Mean ± SD	
MUP amplitude (μV)	143–570	254.1 ± 89.7	114–696	293.1 ± 135.5	p = 0.204
MUP number of turns	127–1552	713.6 ± 359.8	109–1945	651.3 ± 384.6	p = 0.530

AChR = acetylcholine receptor, EDC = extensor digitrum communis, MG = myasthenia gravis, MUP = motor unit potential, MuSK = muscle specific tyrosine kinase, OO = orbicularis oculi, SD = standard deviation, T/A = turns amplitude.