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# Quantitative EMG of facial muscles in myasthenia patients with MuSK antibodies

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**Abstract**

*Objective:* Our aim was to study the pathophysiological process leading to facial muscle atrophy in 13 patients with MuSK antibody positive myasthenia gravis (MuSK-MG), and to compare with findings from 12 acetylcholine receptor antibody positive myasthenia patients (AChR-MG), selected because they suffered from the same degree of disease severity and required similar treatment.
*Methods:* Motor unit action potential (MUAP) and interference pattern analysis from orbicularis oculi (O oculi) and orbicularis oris (O oris) muscles were studied using a concentric needle electrode, and compared with findings in 20 normal subjects, 6 patients receiving botulinum toxin injections (representing a neurogenic model) and 6 patients with a muscle dystrophy (representing a myopathic model). The techniques and control data have been reported previously.
*Results:* The mean MUAP durations for O oculi and O oris were significantly reduced ($p < 0.001$) in both MG cohorts when compared with healthy subjects, and were similar to those in the myopathic control group. They were significantly different from those obtained from the neurogenic control group ($p < 0.001$ for both O oculi and O oris). The MUAP findings in O oculi occurred independently from neuromuscular blocking on single fibre EMG (SFEMG) in the same muscle. On turns amplitude analysis (TAA), 50% of MuSK-MG patients and 42% of AChR-MG patients had a pattern in O oculi which was similar to that in the myopathic control group, and 62% of MuSK-MG patients and 50% of AChR-MG patients had a pattern in O oris that was also similar to that in the myopathic control group. The TAA findings for O oculi and O oris in both MG cohorts were different from those obtained from the neurogenic control group.
*Conclusions:* Facial muscle atrophy in MuSK-MG patients is not neurogenic and the pathophysiological changes are akin to a myopathic process. The selected AChR-MG patients also show evidence of a similar pathophysiological process in the facial muscles albeit to a lesser degree.
*Significance:* We propose that muscle atrophy in MuSK-MG is a myopathic process consisting of either muscle fibre shrinkage or loss of muscle fibres from motor units. The duration of disease and long-term steroid treatment may be further contributory factors.


*Keywords:* Acetylcholine receptor; Facial muscles; Interference pattern; Muscle atrophy; MuSK; Myasthenia gravis; Turns amplitude analysis; Type II muscle fibre

*Abbreviations:* AChR, acetylcholine receptor; AChR-MG, myasthenia gravis associated with antibodies to AChR; Botox, botulinum toxin; CI, confidence interval; CNE, concentric needle electrode; EDC, extensor digitorum communis; EMG, electromyography; FSH MD, facioscapulohumeral muscular dystrophy; Hz, Hertz; IP, interference pattern; Log, logarithm; MA, mean change in amplitude per turn; MD, muscular dystrophy; MG, myasthenia gravis; MGFA, myasthenia gravis Foundation of America score of disease; MRI, magnetic resonance imaging; MUAP, motor unit action potential; MuRF-1, muscle ring finger 1; MuSK, muscle specific tyrosine kinase; MuSK-MG, myasthenia gravis associated with antibodies to MuSK; MyoD, myotonic dystrophy; NMJ, neuromuscular junction; O oculi, orbicularis oculi; O oris, orbicularis oris; SD, standard deviation; SFEMG, single fibre EMG; TAA, turns amplitude analysis; T/s, turns per second.

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## 1. Introduction

Myasthenia gravis (MG) is an acquired immune-mediated condition of the neuromuscular junction (NMJ), which is associated with the presence of antibodies to the muscle nicotinic acetylcholine receptor (AChR) in 85% of patients with generalised disease (AChR-MG). Between 3% and 70% of seronegative MG patients have antibodies to muscle specific tyrosine kinase (MuSK; MuSK-MG) (Hoch et al., 2001; Sanders et al., 2003; Vincent et al., 2004; Zhou et al., 2004; Yeh et al., 2004; Vincent and Leite, 2005). MuSK-MG patients are distinct in that they often have severe and pronounced oculobulbar disease (Scuderi et al., 2002; Sanders et al., 2003; Zhou et al., 2004; Evoli et al., 2003) and some patients may develop wasting of the facial muscles, particularly of the tongue. Wasting of the tongue has been previously described in AChR-MG but this is not a common feature (De Assis et al., 1994). The pathophysiological mechanisms leading to muscle wasting in MuSK-MG are not well understood. Limb muscle biopsies have indicated a myopathic process (Sanders et al., 2003; Evoli et al., 2003) but pathological specimens have not been obtained from clinically-involved facial muscles.

In order to investigate the pathological process leading to and resulting in facial muscle atrophy, we have used quantitative EMG studies in MuSK-MG patients and compared findings with those from AChR-MG patients, who also had severe bulbar disease, and with those from two pathological control groups representing defined diseases that lead to neurogenic or myopathic muscle wasting.

## 2. Methods

### 2.1. Participants and materials

We recruited 13 MuSK-MG patients attending the myasthenia gravis centre in Oxford, UK (age range 21–58, median age of 40) and 12 AChR-MG patients (age range 26–71, median 50.5). The latter group was selected from over 190 case notes, on the basis that they had prominent and persistent bulbar disease with similar requirements for immunosuppressive treatment as the MuSK-MG patients. They were also chosen so that they demonstrated similar age and gender ranges to the MuSK-MG cohort. The electrophysiological findings of these patients were compared with those previously reported (Farrugia and Kennett, 2005) from 20 healthy subjects (9 male and 11 female, age range 22–60 years, mean 39 years), 6 patients receiving regular botulinum toxin injections (to facial, neck or limb muscles) for a dystonic condition (“Botox group”; 1 male, 5 female), and 6 patients with a primary myopathic condition (5 with myotonic dystrophy and 1 with facioscapulohumeral muscular dystrophy; 3 male, 3 female). Subjects consented to the study, which had Oxfordshire Ethical Committee approval (the reference to this is: OxREC 02.224). EMG recordings were performed by a single neurophysiologist (RPK) who was blind to the clinical diagnosis of these patients, using Medelec Synergy Electromyograph and a disposable concentric needle electrode (CNE; TECA™ Accessories Oxford Instruments Medical Old Woking, Surrey, UK) with a diameter of 0.3 mm and recording area of 0.28 $mm^2$ (“facial” needle electrode). Filter settings were maintained between 20 Hz and 10 kHz.

### 2.2. MUAP analysis

We used the method previously described (Farrugia and Kennett, 2005). In brief, minimal recruitment allowed at least 20 motor unit action potentials (MUAPs), with a sharp-rising initial component, to be identified from a quiet baseline and analysed for facial muscles, O oculi and O oris. The MUAP durations were measured using a semi-automatic, semi-manual method, with a fixed display gain of 100 μV per division and a sweep duration of 50 ms (Buchthal et al. (1954a,b) and Buchthal and Rosenfalck, 1955). Amplitudes were measured by an automatic cursor setting and the number of phases for each MUAP was automatically computed.

### 2.3. Interference pattern analysis

We studied the lateral portion of O oculi and the inferolateral fibres of the O oris muscle. After insertion of the CNE, patients were asked to make contractions of various forces from weak to strong, with brief rests in between to avoid muscle fatigue. The force of contraction was not monitored (Farrugia and Kennett, 2005; Stålberg et al., 1983). Data were collected over a total period of 20 s, and stored electronically for later off-line analysis of segments where the subject maintained a sustained contraction, with the sensitivity set between 0.2 and 1 mV per division and a 200 ms epoch length of the EMG trace.

### 2.4. Assessment of facial muscle strength

We assessed the strength of five facial muscles (frontalis, corrugator supercilii, buccinator, O oculi and O oris) and graded each muscle as 0 if normal, 1 if weak but some contraction evident and 2 if severely weak such that no contraction is seen (cumulative score ranging from 0 = normal strength to 10 = complete paralysis). This method has been validated (Farrugia, 2004; Farrugia et al., 2006 b).

### 2.5. Statistical methods

Statistical analysis was performed using GraphPad PRISM 4.0. Non-parametric tests (Dunnett’s multiple comparison tests) were applied in the analysis of MUAP data. For turns amplitude analysis (TAA), we used the criteria applied by Stålberg et al. (1983).