The features of myasthenia gravis with autoantibodies to MuSK

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Myasthenia gravis (MG) is an autoimmune disorder of the skeletal muscles characterised by a decrease in the number of available acetylcholine receptors (AChR). Approximately 80–90% of patients have detectable serum anti-AChR antibodies, but there is conclusive evidence that patients without these antibodies also have an antibody mediated disorder. Recently, it was shown that approximately 40–50% of seronegative MG (SNMG) patients have antibodies to a surface membrane enzyme, muscle specific tyrosine kinase (MuSK), which is responsible for agrin induced AChR clustering at the postsynaptic membrane. A specific clinical phenotype of SNMG has been described in patients with anti-MuSK antibodies, but these antibodies have been also detected in seropositive MG with or without thymoma. We analysed the clinical, electrophysiological, pharmacological, and pathological features in 17 SNMG patients with anti-MuSK antibodies.

METHODS

More than 1200 patients with MG have been treated at the Institute of Neurology, Clinical Centre of Serbia, in Belgrade. In all, the diagnosis of MG was based on a typical clinical pattern, a positive neostigmine and/or edrophonium test and decreasing response on repetitive nerve stimulation (performed on the facial nerve–nasal muscle and auxiliary nerve–deltoid muscle systems) and/or increased jitter in single fibre EMG. During the past 2 years anti-AChR antibodies were assayed in the sera of 276 patients: 221 (80.1%) patients were positive and 55 (19.9%) were negative. Recently, we assayed anti-MuSK antibodies in all seronegative MG patients: 40 women and 15 men. At the time these patients were diagnosed and treated we were unable to perform either anti-AChR Ab or anti-MuSK Ab analyses, thus we did not know the patients’ antibody status. Consequently, all the patients were treated according to the clinical form of the disease, regardless of the presence of antibodies.

The severity of MG was examined at the peak of the disease and graded by using the modified Osserman’s scale and the modified Besinger’s standardised clinical score. Four degrees of muscle weakness were determined. Full muscle strength was graded 0, fatigability 1, moderate to severe weakness 2, and total loss of function 3. The severity of the disease was expressed as the mean disability score (MDS), which was obtained by adding the scores for each of the nine examined muscle groups (extraocular, jaw, facial, bulbar, neck, respiratory, proximal and distal upper limb muscles, and proximal lower limb muscles). In every patient, the MDS was determined at the peak of disease (MDS1) and at the end of the follow up period (MDS2). The outcome was expressed by the mean disability score quotient (MDSQ), which was obtained by MDSQ = MDS2/MDS1. An MDSQ between 0.5 and 1 indicated no improvement, while values between 0 and 0.5 were considered as improvement. Patient was considered to be in remission when MDSQ was 0. Pharmacological remission was defined as the absence of any myasthenic signs with the therapy, and complete remission the absence of any myasthenic signs without any therapy.

The clinical characteristics of anti-MuSK positive patients were compared with those of anti-MuSK negative SNMG patients. All patients have been followed longitudinally for 3–10 years.

The concentration of anti-AChR antibodies was measured by a standard radioimmunoassay method using AChR radioimmunoassay kits (CIS Biointernational). Anti-MuSK antibodies were detected using the MuSK Ab Assay kit (RSR Ltd, Cardiff, UK), according to the manufacturer’s protocol. Briefly, 5 µL of serum was incubated with 50 µL of

Abbreviations: AChR, acetylcholine receptors; MDS, mean disability score; MDSQ, mean disability score quotient; MG, myasthenia gravis; MuSK, muscle specific tyrosine kinase; SNMG, seronegative myasthenia gravis
125I-MuSK (extracellular domains) for 16 hours. Human antibodies were immunoprecipitated for 2 hours, centrifuged, and the washed pellets were measured in a gamma counter.

**Statistical analysis**

For descriptive presentation of numerical and attributive variables, absolute and relative frequencies were calculated. The numerical variables are presented as means (SD). The statistical evaluation of the data was performed using SPSS version 10.0 for Windows. A χ² test with Yates's correction was used to compare the frequency distribution of different gradations of categorical variables in the group of patients with and without anti-MuSK antibodies, and also to compare the difference in the frequency distribution of the same variable between these two groups of patients. Values of p<0.05 were considered to be statistically significant.

**RESULTS**

Among the 55 SNMG patients, 17 were anti-MuSK antibody positive (30.9%) and 38 (69.1%) were anti-MuSK Ab negative. In the group of patients with anti-MuSK antibodies there was a striking prevalence of females. Fifteen patients were women (88.2%) and only two (11.8%) were men (female: male ratio 7.5:1) (χ² with Yates’s correction = 8.4, d.f. = 1, p<0.001). Among anti-MuSK negative SNMG patients there was also a female preponderance (24 females (63.2%) and 14 males (36.8%); female: male ratio 1.7:1), but without statistical significance (χ² with Yates’s correction = 2.2, d.f. = 1, p>0.05). However, the difference in sex distribution between anti-MuSK positive and anti-MuSK negative patients was of no statistical significance (χ² with Yates’s correction = 2.4, d.f. = 1, p>0.05). The age at onset of the anti-MuSK positive MG patients ranged from 22 to 52 years (mean SD (35.6 (10.3) years); in 12 of 17 patients (70.6%), onset of the disease was before the age of 40 years. The age onset of the disease in anti-MuSK negative patients was similar: 38.3 (12.8) years (range 14 to 63 years).

In nine of 17 anti-MuSK positive MG patients (52.9%), the first symptoms of the disease were oculobulbar, in three (17.6%) bulbar, in two (11.8%) ocular, and in the remaining three (17.6%) generalised (χ² = 7.3, d.f. = 3, p>0.05). At the peak of the disease, 14 anti-MuSK positive patients (82.4%) had a severe generalised form of MG (IIIB), and only three patients (17.6%) had the mild generalised form (I) of the disease (fig 1). The majority of the patients shared a similar pattern of muscle weakness, with prevalent involvement of facial and bulbar muscles (in 14 of 17 patients; 82.4%). Six patients (35.3%) developed respiratory muscle weakness and underwent endotracheal intubation with artificial ventilation. In anti-MuSK negative SNMG patients, 11 patients (29%) had the ocular form (I) at the peak of the disease, 17 (44.7%) had the mild generalised form (IIA), and 10 (26.3%) had the severe generalised form (IIIB), according to Osserman’s classification (fig 1). By contrast, anti-MuSK positive patients had more severe forms of the disease (χ² = 15.8, d.f. = 2, p<0.01). In the chronic phase of the disease, three anti-MuSK positive patients (17.6%) developed severe atrophy of facial and lingual muscles, while the same feature was observed in only one anti-MuSK negative patient (2.6%) (χ² with Yates’s correction = 2.15, d.f. = 1, p>0.05). Despite the fact that all patients had generalised muscle weakness, a decreasing response on repetitive nerve stimulation was registered in 18 of 23 anti-MuSK positive patients (47.1%) (fig 2). Single fibre EMG was performed in 11 patients and was positive in all (100%). In anti-MuSK negative SNMG patients, decreasing response on repetitive nerve stimulation was registered in 23 of 27 patients (85.2%) with generalised forms of the disease (fig 2). The sensitivity of repetitive nerve stimulation was significantly lower in anti-MuSK positive patients (χ² with Yates’s correction = 5.6, d.f. = 1, p<0.05).

The effect of neostigmine or edrophonium was negative or equivocal in five anti-MuSK positive patients (29.4%). Five patients (29.4%) had hypersensitive response to usual single dose of pyridostigmine (60 mg) (fig 2). This hypersensitivity was manifested by severe muscle fasciculations, especially in the ocular and facial muscles, blurred vision, hypersalivation, and abdominal cramps. In anti-MuSK negative SNMG patients, hypersensitive response to pyridostigmine was observed in only one patient (2.6%) (χ² with Yates’s correction = 6.0, d.f. = 1, p<0.05) (fig 2). Owing to hypersensitive response to pyridostigmine, all these patients were treated with very small, divided doses of 10–30 mg at every 4–8 hours. The remaining patients received pyridostigmine as doses of 60 mg every 4–8 hours. In addition to anticholinesterases drugs, all anti-MuSK positive and 35 anti-MuSK negative (92%) patients were also treated with corticosteroid drugs (average dose 60 mg of prednisone on alternate day). In the patients who did not respond well to the treatment with anticholinesterases and cortico-steroids, additional immunosuppressive drugs were added. Azathioprine was administered in five anti-MuSK positive

![Figure 1](https://example.com/image1.png) **Figure 1** MG forms (according to Ossermans’ classification) in SNMG patients. p<0.01.

![Figure 2](https://example.com/image2.png) **Figure 2** Hypersensitivity to pyridostigmine and decremental response on repetitive nerve stimulation in SNMG patients. p<0.05.
CONCLUSIONS

Our results indicate that MG with antibodies to MuSK has a different phenotype from the remaining seronegative MG. MG with anti-MuSK antibodies was characterised by a striking prevalence of females (7.5:1), severe, predominantly faciobulbar weakness (82.4%), and more frequent occurrence of facial and lingual muscle atrophy (17.6%). Anti-MuSK MG patients frequently develop hypersensitivity to anticholinesterase drugs (29.4%). Thymus pathology is less common in this subgroup of patients, but thymectomy is still beneficial. Routine repetitive nerve stimulation test has a
low, while single fibre EMG has very high sensitivity. The specific clinical, electrophysiological, and immunological presentation, the thymus pathology, and the therapeutic response, particularly to anticholinesterase drugs, implicate that MG with anti-MuSK antibodies is a specific subgroup of seronegative MG. This emphasises the predictive value of anti-MuSK antibody analysis in all seronegative MG patients.

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