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Myasthenia Gravis Patients with Anti-MuSK Antibodies

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A B S T R A C T

In myasthenia gravis *(MG) patients without detectable anti-acetylcholine receptor (anti-AChR) antibody, referred to as seronegative* myasthenia gravis *patients, there is a variable proportion of patients with antibodies against the muscle-specific kinase (MuSK). MuSK antibodies were found in 8 (29.6%) of our 27 patients with generalized MG without anti-AChR antibodies. All these patients were female. The age at the onset ranged from 22 to 38 years. All patients had ocular and bulbar symptoms, and two patients also had generalized limb weakness. Two patients had pure ocular symptoms for 7 or 8 years before the development of bulbar symptoms. All anti-MuSK positive patients were treated with immunosuppressive drugs, three received plasmapheresis and one patient required mechanical ventilation. Our results are consistent with other literature reports.*

Key words: myasthenia gravis*, anti-MuSK antibody, MuSK positive* myasthenia gravis

Introduction

Myasthenia gravis (MG) is an autoimmune disease affecting neuromuscular junction, which results in impairment of neuromuscular transmission with clinical features of weakness and fatigue. Autoantibodies to acetylcholine receptors in serum are detected in 80%–90% of patients with generalized MG (AChR-MG)[1]. AChR antibodies reduce the number of avaliable postsynaptic AChRs. About 10%–20% of patients with generalized MG do not have antibodies to AChR and they are referred to as seronegative MG (SNMG) patients. However, a number of these patients (22%–70%) have antibodies against the muscle-specific kinase (MuSK, MuSK-MG)[2–13]. Interestingly, in Norway no such patient had been identified before 2005[14].

We report on our patients with anti-MuSK antibodies, with special reference to their clinical characteristics.

Patients and Methods

We present eight seronegative MG patients with positive anti-MuSK antibodies, treated at Department of Neuromuscular Diseases, Department of Neurology, University Hospital Center Zagreb in Zagreb. The diagnosis of MG was based on clinical recognition of typical myasthenic symptoms with diurnal variation and pharmacological testing (acetylcholinesterase inhibitor injection). Electrophysiological study (repetitive nerve stimulation) was performed in six patients. Three patients had mildly positive test, whereas three patients had normal findings.

The anti-AChR antibodies were testing using standard radioimmunoassay of serum samples, with values below 0.2 nmol/L considered negative. The anti-MuSK antibodies were tested using standard radioimmunoassay of serum samples in Oxford, UK (Professor Angela

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Vincent, Neurosciences Group, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford University). Testing for antibodies was performed from June 2005 to October 2007.

Results

Anti-MuSK antibodies were present in eight (29.6%) of 27 patients with anti-AChR-antibody-negative MG. None of the patients with anti-AChR antibodies had anti-MuSK antibodies. All MuSK positive patients were women. The age at onset ranged from 22 to 39 years. Demographic and clinical characteristics of MG patients with positive anti-MuSK antibodies are shown in Table 1. All patients were treated with pyridostigmine, with minimal response in two patients. Immunosuppressive drugs were added according to current indications in all patients and proved efficacious. All anti-MuSK positive patients were treated with immunosuppressants, three received plasmapheresis and one patient required mechanical ventilation at the onset of MG. All patients had ocular and bulbar symptoms, and two patients also showed symptoms of generalized MG. Two patients had pure ocular symptoms for 7 or 8 years before the occurrence of bulbar symptoms.

One patients suffering from chronic MG for 33 years had overt hypotrophy of limb muscles. Muscle atrophy was not observed in other patients.

Discussion

Hoch et al. found antibodies to a membrane-linked muscle-specific kinase in sera of 17 of 24 patients with seronegative MG[2]. MuSK is a transmembrane polypeptide expressed in skeletal muscle localized predominantly on the postsynaptic membrane of the neuromuscular junction. Although MuSK is very important in muscle development, its role in mature muscles has not yet been fully clarified. Antibodies to MuSK have been identified in sera of 22–70% of seronegative MG patients[2–13], but not in sera with positive AChR antibodies. In Norway, none had been identified before 2005[14]. Clinically, it was soon recognized that the absence of anti-AChR antibodies did not necessarily mean mild disease. Severe symptoms requiring immunosuppressive therapy are reported to be similar, or may even be more frequent, in patients with anti-MuSK antibodies. While their main clinical characteristic, muscle fatique, is similar to those in patients with anti-AChR antibodies, their weakness more commonly and more severely involves oculobulbar, neck

TABLE 1
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH ANTI-MuSK POSITIVE MYASTHENIA GRAVIS

Patient No. Sex Year of birth	Age at onset (yrs)	Duration (yrs) to the last follow up	Symptoms to the last follow up	Therapy Pyridostigmine +	Thymectomy – thymus	Follow up
1 F 1976	24	7	Ocular, bulbar/speech	Corticosteroids Plasmapheresis	–	Periodical exacerbation
2 F 1970	32	5	Bulbar	Corticosteroids periodically	+ »normal« thymus	Improvement post-thymectomy, stable remission
3 F 1954	20	33	Ocular at onset, bulbar, limb weakness	Corticosteroids	+ No data on thymus	Chronic disease with limb and bulbar weakness; hypotrophy of limb muscles
4 F 1949	39	18	Ocular, bulbar, respiratory weakness	Corticosteroids	–	Acute onset with bulbar and respiratory symptoms needing assisted ventilation; later, two episodes of exacerbation with bulbar symptoms; now stable for 5 yrs
5 F 1973	22	12	Ocular, bulbar	Corticosteroids Azathioprine Plasmapheresis	–	Ocular symptoms for 8 yrs; periodically bulbar symptoms in the last 4 yrs
6 F 1976	24	7	Bulbar, ocular, generalized weakness	Corticosteroids Azathioprine Plasmapheresis	–	Periodical exacerbation (stress)
7 F 1955	32	20	Ocular, bulbar	Corticosteroids	–	Stable improvement with low steroid dose
8 F 1959	38	10	Ocular, bulbar, neck muscles	Corticosteroids	–	Periodically pure ocular symptoms; in 2005 and 2007, bulbar and neck weakness

and respiratory muscles, and respiratory crises are also more common. Several clinical studies on MuSK-MG have been published, showing that this MG subset has a clearly clinical pattern[3–6,8–13].

Evoli et al. have described clinical phenotype in 37 patients with positive MuSK antibodies. In their study, female patients predominated (n=29). Age at onset ranged from 6 to 68 years, with 56.8% of patients presenting below 40 years of age[3].

Sanders et al. describe clinical aspects in 12 (38%) of 32 seronegative MG patients with disease onset at age 21–59. The response to acetylcholinesterase inhibitors was variable. All patients improved after plasmapheresis, and most had good response to immunosuppressive therapy[8].

Zhou et al. compared clinical findings of patients with positive MuSK antibodies and other seronegative patients. They noticed that neck muscles were commonly involved in anti-MuSK positive patients and limb muscles in seronegative patients (without AChR or MuSK antibodies). The responses to anti-cholinesterase and immunosuppressive treatment were similar[9]. Lavrnic et al. found the majority of patients with anti-MuSK antibodies to have predominant involvement of facial and bulbar muscles (82.4% of 17 patients). There was also a high prevalence of female patients (15 of 17). One third of them did not respond well to anti-cholinesterase drugs[5].

Our group of patients with anti-MuSK antibodies was characterized by high prevalence of female patients with age at onset of MG ranging from 23 to 28 years. This finding was consistent with literature data. Approximately 50% of patients with ocular MG have anti-AChR antibodies. Anti-MuSK antibodies are very rarely present in pure ocular MG, although most patients first present with mainly ocular symptoms[15]. Indeed, two of our patients had pure ocular symptoms for 7 or 8 years before the development of bulbar symptoms. Interestingly, however, Ishii et al. report on a patient with anti-MuSK positive MG that showed progressive muscular atrophy and weakness in bulbar region and upper extremities without ptosis during 22-year clinical course[16]. One of our patients suffering from MG for 33 years had hypotrophy of limb muscles.

There is no clear evidence for the efficacy of thymectomy in anti-MuSK positive patients, possibly because only few patients have been thymectomized[3,6–11]. Similarly, in our study, we could not make any definite conclusion on the clinical benefits of thymectomy because only two of our patients were thymectomized and one of them reached stable remission. The histopathologic finding in this patient was »normal« thymus. The other thymectomized patient had undergone thymectomy 30 years before and no relevant data on the histopathologic finding in thymus tissue were available. More prospective controlled studies will hopefully shed more light on the issue in the future.

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MIASTENIJA GRAVIS KOD BOLESNIKA S POZITIVNIM PROTUTIJELIMA NA MuSK

S A Ž E T A K

Bolesnici s miastenijom gravis (MG) kod kojih se ne nađu protutijela na acetilkolinske receptore (AChR) referiraju se kao bolesnici sa seronegativnom miastenijom gravis. Ti bolesnici u različitom postotku imaju pozitivna protutijela na specifičnu mišićnu kinazu (MuSK). Protutijela na MuSK bila su pozitivna kod 8 od 27 naših bolesnika s MG (29,6%) kod kojih nisu nađena protutijela na AChR. Svi naši bolesnici su bile žene. Simptomi MG su se javili u dobi od 22–38 godina. Sve bolesnice su imale očne i bulbarne simptome, a dvije su imale i generaliziranu slabost u rukama i nogama. Dvije su bolesnice imale samo okularne simptome 7 odnosno 8 godina prije pojave bulbarnih simptoma. Sve su liječene imunosupresivnom terapijom, tri su bolesnice liječene plazmaferezom, a jedna je u jednom razdoblju trebala i mehaničku ventilaciju. Naši rezultati su slični rezultatima ostalih autora.