ABSTRACT: We assayed cryopreserved sera from 38 acetylcholine receptor (AChR) antibody-negative patients with myasthenia gravis (MG) who were followed clinically for muscle-specific tyrosine kinase (MuSK) antibodies and analyzed and compared their clinical characteristics. None of 13 sera from patients with purely ocular MG were positive. Sera from 10 of 25 patients (40%) with generalized MG were positive for MuSK antibodies. The age at onset of myasthenic symptoms was significantly earlier in MuSK antibody-positive patients ($P = 0.02$). MuSK antibodies were present in AChR antibody-negative patients of either gender, with virtually identical prevalence in women (41.2%) and men (37.5%). The distribution of weakness more commonly involved neck muscles in MuSK antibody-positive patients, and limb muscles in MuSK antibody-negative patients. Patients responded to immunosuppressive treatment regardless of whether MuSK antibody was present. We conclude that MuSK antibodies are present and diagnostically useful in a subset of myasthenic patients without AChR antibodies. Although the distribution of weakness differs somewhat depending on whether MuSK antibodies are present, responses to anticholinesterase and immunosuppressive treatments are similar.

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CLINICAL COMPARISON OF MUSCLE-SPECIFIC TYROSINE KINASE (MuSK) ANTIBODY-POSITIVE AND -NEGATIVE MYASTHENIC PATIENTS

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Myasthenia gravis (MG) is due to a deficit of nicotinic acetylcholine receptors (AChRs) at neuromuscular junctions, which results in impairment of neuromuscular transmission, with clinical features of weakness and fatigue.[5] Autoantibodies to AChR are detected in the sera of 80–90% of patients with generalized MG using sensitive radioimmunoprecipitation assays,[15,17,26] and several mechanisms by which these antibodies reduce the number of available postsynaptic AChRs have been described in detail and reviewed.[6,7] The absence of detectable AChR antibodies in sera of more than 10–20% of MG patients has been difficult to understand.[20,24,25] However, there is persuasive evidence that circulating pathogenic autoantibodies are also present in these patients, and are responsible for the myasthenic abnormalities. Thus, most AChR antibody-negative patients respond favorably to plasmapheresis or immunosuppression.[11,20] Sera from these patients contain antibodies that bind to mammalian skeletal muscle.[1,2,23] Passive transfer of immunoglobulin from AChR antibody-negative sera to mice has been shown to result in a reduction of miniature endplate potential amplitudes in the recipient animals.[3,8,9,20]

Recently, antibodies to muscle-specific kinase (MuSK), a receptor tyrosine kinase that in mature muscle is localized predominantly on the postsynaptic membrane of the neuromuscular junction, have been identified in sera from 40–70% of myasthenic patients without AChR antibodies, but not in sera from those with AChR antibodies.[12,14,22] These anti-MuSK antibodies have been shown to bind to MuSK

Abbreviations: AChR: acetylcholine receptor; IgG, immunoglobulin G; MG, myasthenia gravis; MuSK, muscle-specific tyrosine kinase
Key words: acetylcholine receptor antibody; acetylcholine receptor antibody-negative myasthenic patients; clinical characteristics; MuSK antibody; myasthenia gravis
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Table 1. Clinical information of patients with generalized AChR antibody-negative MG.

Case	MuSK-Ab	Gender	Age at onset (years)	Duration (years)	MGFA classification		Immunosuppressive treatment*
					At diagnosis	At last visit	
1	Positive	M	49	5	IIIb	PR	None
2	Positive	F	32	6	IIIb	IIb	Prednisone
3	Positive	F	31	3	IIIb	IVb	None
4	Positive	F	60	13	IIIa	IIa	None
5	Positive	F	35	2	IIa	IIa	None
6	Positive	M	40	14	IVb	IIb	Prednisone
7	Positive	M	44	2	IIIb	IIb	None
8	Positive	F	5	9	IIIb	IIb	None
9	Positive	F	30	10	IIIa	IIa	None
10	Positive	F	20	23	IIb	IIb	Prednisone
11	Negative	F	65	8	I	IIa	Prednisone
12	Negative	F	54	5	IIIa	PR	None
13	Negative	M	41	1	IVb	IIb	Cyclosporine, mycophenolate, prednisone
14	Negative	F	58	12	IVb	IIa	Azathioprine
15	Negative	F	56	2	IIa	IIa	None
16	Negative	M	38	22	IIIb	IIa	Prednisone
17	Negative	F	46	4	I	IIb	Cyclosporine
18	Negative	F	67	3	IIb	IIb	None
19	Negative	F	44	21	IIb	IIIb	None
20	Negative	M	64	2	IIb	IIb	None
21	Negative	F	21	6	IIIb	PR	None
22	Negative	M	26	7	IIIa	IIIa	None
23	Negative	F	57	7	IIa	IIa	None
24	Negative	M	58	4	IIa	IIa	None
25	Negative	F	34	4	IIIb	IIIb	Prednisone, mycophenolate

MGFA, Myasthenia Gravis Foundation of America Clinical Classification[16]; PR, pharmacological remission.
**Immunosuppressive agents received when blood was drawn.*

in vitro, and to inhibit agrin-induced clustering of AChRs in cultured muscle cell lines. Although the role of anti-MuSK antibodies in the pathogenesis of MG is not yet clear, their presence in serum is specific for AChR antibody-negative MG, and therefore should be useful as a diagnostic test in patients who lack AChR antibodies. In this study we report the clinical characteristics of 25 such patients with generalized MG and compare the features of patients with MuSK antibodies to those without such antibodies. None of 13 patients with purely ocular AChR antibody-negative MG had MuSK antibodies. Our data may help the treating physician to identify this group of patients and to use appropriately the MuSK antibody test which is now available commercially (Athena Diagnostic Laboratory, Worcester, MA).

MATERIALS AND METHODS

Patient Identification. Thirty-eight AChR antibody-negative myasthenic patients were identified by searching the Johns Hopkins Neuromuscular Unit database for patients who fulfilled the criteria for MG, and had AChR antibody radioimmunoassay tests performed at our institution from January 1996 to December 2002. All patients in this analysis (Table 1) manifested typical clinical features of MG and were without AChR antibodies (i.e., <0.3 nM). Positive diagnostic features of MG also included one or more of the following: decremental response of $>10\%$ on repetitive nerve stimulation; abnormal jitter or blocking on single-fiber EMG (SFEMG); and an unequivocally positive response to edrophonium or other anticholinesterase agents. Some patients also had beneficial responses to immunomodulatory treatments.

Detection of MuSK Antibody. Sera originally submitted to the Neuromuscular Serology Laboratory for AChR antibody determination were aliquoted and stored at $-80°C$. Frozen sera obtained at the time of initial presentation to our institution were tested for MuSK antibodies by radioimmunoassay, as described previously.[22] At the time of sampling, 3 of 10 MuSK antibody-positive patients, and 6 of 15 antibody-nega-

Table 2. Clinical weakness in patients having generalized myasthenia gravis without acetylcholine receptor antibodies.

	Initial weakness			Weakness			Predominant weakness		
	MuSK antibodies			MuSK antibodies			MuSK antibodies		
Muscle group	Present (n = 10)	Absent (n = 15)	P-value	Present (n = 10)	Absent (n = 15)	P-value	Present (n = 10)	Absent (n = 15)	P-value
Ocular	6 (60%)	11 (73.3%)	0.67	9 (90%)	15 (100%)	0.40	4 (40%)	9 (60%)	0.43
Bulbar	3 (30%)	2 (13.3%)	0.36	7 (70%)	11 (73.3%)	1.00	4 (40%)	2 (13.3%)	0.18
Neck	0	0	N/A	7 (70%)	5 (33.3%)	0.11	0	0	N/A
Respiratory	2 (20%)	0 (0%)	0.15	7 (70%)	8 (53.3%)	0.68	2 (20%)	1 (6.7%)	0.54
Limb	1 (10%)	2 (13.3%)	1.00	6 (60%)	15 (100%)	0.02	1 (10%)	5 (33.3%)	0.20

Differences in the proportion of subjects presenting with clinical weakness were assessed using Fisher's exact test. MuSK, muscle-specific tyrosine kinase.

tive patients with generalized MG were being treated with various immunosuppressive agents (Table 1).

Clinical Characterization of AChR Antibody-Negative Myasthenic Patients. Clinical data were abstracted from physicians' detailed notes on each patient, and entered into a Microsoft Access database. The data were stratified on the basis of MuSK serostatus. Because continuous measures were not normally distributed, the results are presented as medians and interquartile ranges (25th and 75th percentile of the distribution). Differences between the MuSK-positive and -negative groups on these measures were analyzed using a nonparametric test statistic, the Wilcoxon rank sum test. All categorical measures are presented as contingency tables, and differences between the two groups were analyzed using Fisher's exact test to account for the paucity of data in some classifications.

In view of the exploratory nature of this analysis, significance levels were not adjusted for multiple comparisons. The aim was to determine the level of variability in these measures that was accounted for by knowing the MuSK serostatus of these patients. All clinical measures that were identified in the exploratory phase were tested simultaneously using a logistic regression model. This method determines the likelihood of an outcome, that is, MuSK-positive serology, given a clinical feature, such as a favorable response to treatment.

RESULTS

Patient Characteristics. Thirteen patients had localized ocular MG and 25 patients had generalized MG (Table 1). None of the patients with ocular MG had detectable MuSK antibodies. Ten patients with generalized MG (40%) had MuSK antibody-positive sera, including 3 men and 7 women. Among the 25 patients with generalized MG but no AChR antibodies, MuSK testing was positive in 3 of 8 men (37.5%) and 7 of 17 women (41.2%). The age of onset in the MuSK antibody-positive group ranged from 5 to 60 years (median 33.5 years; interquartile range 30–44). The age of onset in the MuSK antibody-negative group was significantly later, ranging from 21 to 67 years (median 54 years; interquartile range 38–58; $P = 0.04$). Table 1 indicates the severity of MG at the time of diagnosis and at the last clinical contact for each patient.

Clinical Weakness. We analyzed the patterns of weakness in our AChR antibody-negative patients with generalized MG, and compared the initial presentation, regions affected, and predominant weakness in patients with and without MuSK antibodies (Table 2). Predominant weakness was defined as the most severely affected muscle group or groups at the time of maximum weakness.

In the MuSK antibody-positive group, the weakness initially involved the extraocular muscles in 6 of 10 (60%) patients, bulbar muscles in 3 (30%), respiratory muscles in 2 (20%), and limb muscles in 1 (10%). During the disease course, the weakness affected the ocular muscles in 9 (90%), bulbar muscles in 7 (70%), respiratory muscles in 7 (70%), neck muscles in 7 (70%), and limb muscles in 6 (60%). The predominant weakness was ocular in 4 (40%), bulbar in 4 (40%), respiratory in 2 (20%), and limb in 1 (10%).

In the MuSK antibody-negative group, the weakness initially involved extraocular muscles in 11 of 15 (73.3%), bulbar muscles in 2 (13.3%), and limb muscles in 2 (13.3%). During the disease course, the weakness affected the extraocular muscles in all 15 (100%), bulbar muscles in 11 (73.3%), respiratory muscles in 8 (53.3%), neck muscles in 5 (33.3%), and limb muscles in 15 (100%). The predominant

weakness was ocular in 9 (60%), bulbar in 2 (13.3%), respiratory in 1 (6.7%), and limb in 5 (33.3%).

Thus, the MuSK antibody-positive group demonstrated a tendency toward a higher proportion of patients with neck weakness (Fisher's exact test, $P = 0.11$), whereas the MuSK antibody-negative group had a significantly greater proportion of patients with limb weakness (Fisher's exact test, $P = 0.02$). There were no significant differences between groups with respect to the proportion demonstrating weakness in any of the other muscle groups.

Treatment Response. The responses to anticholinesterase and immunomodulatory agents of patients in the MuSK antibody-positive and -negative groups were similar, and generally successful. Cholinesterase inhibitors were used initially in most patients. Three of 10 patients (30%) in the MuSK antibody-positive group and 8 of 15 (53.3%) in the MuSK antibody-negative group responded to pyridostigmine, and continued to take it throughout their course. Pyridostigmine monotherapy produced satisfactory results in 3 of 4 patients in the MuSK antibody-negative group, but the response to anticholinesterase agents did not differ in the two groups.

Because this study was retrospective, immunomodulatory treatment was carried out without a predetermined protocol, and virtually all patients were treated with and responded well (Table 1) to various combinations of immunosuppressive agents, including prednisone, azathioprine, cyclosporine, mycophenolate, intravenous immunoglobulin, plasmapheresis, and high-dose cyclophosphamide.[10] Therefore, the responses of the two patient groups to individual treatment modalities cannot be compared. Likewise, the effects of thymectomy, performed in 6 of 10 patients with positive MuSK antibodies and 3 of 15 without such antibodies, cannot be evaluated. Histopathological reports were available for thymus tissue from all 6 of the MuSK antibody-positive patients, and 3 of the MuSK antibody-negative patients. Thymus glands from 1 of 6 MuSK antibody-positive patients, and 2 of 3 MuSK antibody-negative patients showed lymphoid hyperplasia.

DISCUSSION

Consistent with previous reports,[12,14,22] we found that MuSK antibody was present in sera from a significant proportion of patients with generalized AChR antibody-negative MG, but not in those with MG restricted to the extraocular muscles. Hoch et al. reported that none of 39 patients with AChR antibody-positive MG, and none of 33 patients with other neurological diseases had positive anti-MuSK antibodies.[14] Therefore, when the MuSK-antibody test is positive, it is a useful diagnostic indicator of MG in AChR antibody-negative patients with generalized myasthenic weakness. However, in patients with purely ocular features, who often present difficult diagnostic problems, it is not helpful.

The MuSK antibody-positive rate in our patients with generalized MG and no AChR antibodies was 40%, consistent with the figures of 40% and 47% recently reported,[12,22] but lower than the 70% positivity rate that was originally published.[14] Clearly, a negative MuSK antibody test does not exclude MG. Because 6 of the 15 MuSK antibody-negative patients were treated with immunosuppressive agents at the time their sera were obtained, it is theoretically possible that this may have resulted in false-negative results in some cases, similar to the loss of detectable AChR antibody that we have observed following immunosuppression in some initially AChR antibody-positive myasthenic patients. Ideally, testing for MuSK antibody should be performed before the initiation of immunosuppressive therapy to assess the antibody-positive rate more accurately. In our series, anti-MuSK antibody was present in both male (3 of 8; 37.5%) and female (7 of 17; 41%) patients with AChR antibody-negative MG, in virtually identical proportions. In other studies, the proportions of MuSK antibody-positive females were higher.[12,22]

The initial symptoms involved the extraocular muscles in the majority of patients, both in the MuSK antibody-positive group (60%) and the MuSK antibody-negative group (73.3%), as is also true for AChR antibody-positive patients.[5] In the MuSK antibody-positive group, bulbar muscles were involved initially in 30% and respiratory muscles in 20%; these trends were slightly higher than in the MuSK antibody-negative group although they did not reach statistical significance. During the disease course there was a trend for neck weakness to occur more commonly in the MuSK antibody-positive group (70%) than in the MuSK antibody-negative group (33.3%; $P = 0.11$), although it was not disabling in any patients. The weakness involved either neck extensors or neck flexors, or both. By contrast, limb weakness was significantly more common in the MuSK antibody-negative group (100%) than in the MuSK antibody-positive group (60%; $P = 0.02$). About 40% of MuSK antibody-positive patients did not have any limb weakness and, in these patients, the weakness was confined to the oculobulbar, neck, or respiratory muscles. The predominant weakness in the MuSK antibody-positive patients affected the

bulbar (40%) and respiratory (20%) muscles more frequently than in the MuSK antibody-negative patients (13.3% and 6.7%, respectively). Previous reports have described high frequency and predominance of bulbar, respiratory, and neck weakness in MuSK antibody-positive patients.[12,22] Although permanent facial weakness with some facial muscle atrophy was described in many MuSK-positive patients in a previous report,[12] this was not a distinct feature in our patients. Among our 10 MuSK antibody-positive patients, only 5 had detectable facial weakness on their last clinical visits; the weakness was moderate (grade 4− on the Medical Research Council Scale) in 2, and mild (grade 4+) in 3. Mild facial weakness was also seen in 6 of 15 MuSK antibody-negative patients.

The response of our MuSK antibody-positive patients to anticholinesterase agents and to immunomodulatory treatments was very similar to the responses of MuSK antibody-negative or AChR antibody-positive myasthenic patients. The present data do not permit statistical analysis of the relative effectiveness of the different modalities used. However, our clinical experience, and that of others,[22,23] suggests that the immunosuppressive agents currently in use for conventional AChR-positive MG are also effective in MuSK antibody-positive or -negative MG. The finding of histological evidence of lymphoid hyperplasia in one of the MuSK antibody-positive and two of the MuSK antibody-negative patients raises the possibility that thymectomy may be of benefit in a subset of these patients. However, final judgment regarding the effect of thymectomy in these patients should be reserved until the results of a prospective study are available.

There is substantial clinical and experimental evidence that AChR antibody-negative MG is due to an antibody-mediated autoimmune process. As in patients with conventional MG, motor point biopsies from all,[8,9] or nearly all,[25] AChR antibody-negative MG patients tested showed significantly reduced numbers of AChRs at neuromuscular junctions; plasmapheresis or immunosuppressive treatment resulted in clinical improvement.[11,20] Passive transfer of immunoglobulin G (IgG) from AChR antibody-negative MG patients to mice resulted in reduced miniature endplate potential amplitudes,[3,8,9,20] and a reduction of AChRs at neuromuscular junctions of recipient mice in some studies.[8,9] Transient neonatal MG, which results from transfer of antibodies from mother to fetus, has been described in one case of AChR antibody-negative MG.[19] Serum IgG from such MG patients binds to mammalian skeletal muscle cells in culture.[1,2,23] This evidence strongly supports the role of a humoral factor, presumably immunoglobulin, in the pathogenesis of MG in these patients. However, the pathogenic role of the identified anti-MuSK IgG antibody is not yet clear. MuSK is a protein with tyrosine kinase activity, which is normally localized at the neuromuscular junction, and in concert with agrin plays a key role in aggregation of AChRs and postsynaptic differentiation.[13,18] Because anti-MuSK antibodies inhibit agrin-induced clustering of AChRs in cultured muscle cells,[14] it has been suggested that they may interfere with AChR localization in AChR antibody-negative MG. However, recent studies have suggested that sera from such MG patients may exert a transient inhibitory effect on AChRs that appears to be independent of either the IgG fraction or MuSK antibody itself.[21] It is of interest that a non-IgG serum factor has also been detected in MG sera without AChR antibodies.[27] Whether anti-MuSK IgG plays a direct role in the pathogenesis of MG will require additional studies to meet criteria for antibody-mediated autoimmune diseases, as previously outlined.[4] At present, the finding of anti-MuSK antibodies provides evidence that autoantibodies directed at components of the neuromuscular junction other than the AChR are present in MG. From a clinical point of view, a positive anti-MuSK antibody test appears to be a reliable diagnostic indicator of MG in AChR antibody-negative patients with generalized symptoms of myasthenia. However, the patients' clinical features do not clearly distinguish MuSK antibody-positive from MuSK antibody-negative serotypes.

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