

MuSK (Muscle Specific Kinase) Positive Myasthenia: Grave Prognosis or Undue Prejudice?

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Abstract

Objectives: Patients with muscle-specific kinase (MuSK)-positive myasthenia are generally considered to have a grave prognosis. We present our experience of patients with myasthenia with different antibody status. This is followed by a short discourse on previous studies and the current view on MuSK-positive myasthenia, focusing on the associated prejudice. **Materials and Methods:** This study compares 23 patients with MuSK-positive myasthenia with 55 patients with acetylcholine receptor-positive myasthenia and 9 patients with double-seronegative myasthenia at a tertiary level center. **Results:** We did not find any significant difference in terms of clinical characteristics, treatment response to immunosuppressants, long-term prognosis, and quality of life. **Conclusion:** Seropositivity for antibodies should not be used in isolation to guide the management or predict the prognosis. Undue negative prognostication may affect the morale of patient. Clinical features and response to therapy in addition to antibody status must be considered before planning therapy.

Keywords: MuSK, myasthenia, prognosis, quality of life, rituximab

INTRODUCTION

Since the first description of muscle-specific kinase (MuSK)-positive myasthenia (MuSK+ve MG) by Hoch *et al.* in 2001,^[1] there have been multiple descriptions of clinical features of these patients. MuSK+ve MG are considered to have a more turbulent course at the beginning, and more severe symptoms at onset than acetylcholine receptor positive myasthenia (AChR+ve MG).^[2] Neurologists tend to treat MuSK+ve MG more aggressively than AChR+ve MG. There has been much speculation about the utility of antibody status (acetylcholine receptor antibody positive (AChR+ve) vs MuSK antibody-positive) in prognostication and planning therapy.^[3]

AIM OF THE STUDY

This is a single-center, ambispective, comparative study comparing demographic and clinical characteristics, treatment response, and outcome of MuSK+ve MG with AChR+ve MG and patients with double-seronegative myasthenia (DN-MG).

MATERIALS AND METHODS

A retrospective chart review of MuSK+ve MG presenting to our institute from January 2010 to January 2016 was performed. All consecutive MuSK+ve MG who presented to our institute from February 2016 to July 2017 were also recruited. Demographic data, clinical details, and investigations were recorded. The diagnosis of myasthenia was made based on clinical, electrophysiological, and serological findings. All the antibody testing (anti-AChR or anti-MuSK) was done by

radioimmune assay. The severity of disease and response to therapy were recorded according to Myasthenia Gravis Foundation of America (MGFA) recommendations. Response to treatment and outcome analysis were done only in those patients with adequate follow-up. Poor outcome was defined as one or more of the following: (1) postintervention status: unchanged, worse, exacerbation, death from MG; (2) inability to achieve low maintenance dose of pyridostigmine or steroids; (3) intravenous immunoglobulin (IVIg) or plasmapheresis (PLEX) on a regular basis. Quality-of-life assessment was done by MGQoL15r questionnaire. (4) Severe disease was defined as MGFA IV or MGFA V. Low maintenance treatment was defined as pyridostigmine ≤ 120 mg and prednisolone with a dose reduction by $\leq 50\%$ from the maximum dose. Good response to acetylcholine-esterase inhibitors (AChEIs) was defined as more than 50% improvement.

Statistical analysis was done using STATAIC/11.1. Comparison of means/medians/proportions among three groups was done. The association between antibody type and patient outcome was analyzed by logistic regression. Significance was set at $P \leq 0.05$.

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DOI: 10.4103/aian.AIAN_302_19

RESULTS

In this study, 23 MuSK+ve MG, 55AChR+ve MG, and 9 DN patients were included [Table 1]. All the three groups were comparable to each other in terms of duration of illness and associated comorbidities. The proportion of females in MuSK+ve MG (69.6%) was significantly higher than that in AChR+ve MG (41.8%) ($P = 0.02$). There was no significant difference between the three groups in terms of age of onset, bulbar symptoms at onset, median interval between the first symptom and diagnosis, diurnal variation, positive neostigmine test, and positive repetitive nerve stimulation test. Thymic hyperplasia on contrast-enhanced computed tomography chest was significantly higher in AChR+ve MG (41.3%) than MuSK+ve MG (13.3%) ($P = 0.04$). The average number of myasthenic crisis per patient-year was not significantly different between the three groups ($P > 0.99$).

None of the patients in any group had severe disease (MGFA IV or V) at onset. Figure 1 shows the distribution of patients according to MGFA classification at disease onset, maximum

severity of disease, and at the time of last follow-up. No significant difference between the three groups was observed.

Good response to AChEI was similar in all groups. A significantly larger proportion of patients in MuSK+ve MG (84.2%) were prescribed both AChEI and steroids from the beginning compared with AChR+ve MG (37.2%) ($P < 0.0005$) [Table 2]. The maximum dose and incidence of adverse effects of AChEI or steroids were similar in three groups. Logistic regression analysis did not reveal any significant difference in incidence of adverse effects after adjusting for age, maximum dose, and duration of medication.

Eighteen MuSK+ve MG, 40 AChR+ve MG, and 5 DN-MG patients were on azathioprine [Table 3]. There was no significant difference between them in terms of proportion of time on azathioprine compared with total duration of follow-up, maximum dose of azathioprine, incidence of adverse effects, or poor outcome.

Two MuSK+ve MG and six AChR+ve MG patients were given rituximab [Table 3]. Both MuSK+ve MG and five

Table 1: Comparison of demographic, clinical characteristics, and investigations of patients with MuSK+ve MG with patients with AChR+ve MG and patients with double-seronegative MG

	MuSK-positive MG (n=23)	AChR-positive MG (n=55)	Double-seronegative MG (n=9)	p1 [#]	p2 ^{##}
Current age (years), median (range)	49 (15-68)	43 (18-81)	39 (18-75)	0.39	0.57
Sex*				0.08	0.05
Male, n (%)	7 (30.4)	32 (58.2)	5 (55.6)		
Female, n (%)	16 (69.6)	23 (41.8)	4 (44.4)		
Duration of disease (years), median (range)	4 (0.5-19)	3.5 (0.33-30)	3 (1-19)	0.90	0.69
Other comorbidities, n (%)				0.39	0.84
Hypothyroidism	3 (13.0)	12 (21.8)	1 (11.1)		
Hyperthyroidism	0	1 (1.8)	0		
Vascular risk factors	8 (34.7)	15 (27.3)	1 (11.1)		
Autoimmune illnesses	3 (13.0)	1 (1.8)	0		
Infectious disease	2 (8.7)	2 (3.6)	0		
Age at onset, median (range)	44 (14-66)	35 (8-76)	20 (14-65)	0.34	0.52
First symptom at onset, n (%)				0.31	0.11
Ocular	8 (34.8)	29 (53.7)	7 (77.8)		
Bulbar**	11 (47.8)	15 (27.8)	1 (11.1)		
Limb	4 (17.4)	9 (16.7)	1 (11.1)		
Respiratory	0	1 (1.9)	0		
Reported symptoms during illness				0.12	0.10
Pure ocular	0	3	1		
Oculobulbar	5	4	2		
Generalized	18	48	6		
Interval between first symptom and diagnosis (months), median (range)	4 (0.3-72)	4 (0.25-192)	3 (0.25-48)	0.51	0.32
Patient with diurnal variation, n (%)	18/23 (78.2)	46/53 (86.8)	9/9 (100)	0.57	0.65
Patients (%) with positive neostigmine test	10/13 (76.9)	28/29 (96.6)	6/7 (85.7)	0.07***	0.12
Patients (%) with positive RNST	17/18 (94.7)	39/43 (90.7)	7/9 (77.8)	0.35	0.88
Patients (%) with thymic hyperplasia on imaging*	2/15 (13.3)	19/46 (41.3)	2/6 (33.3)	0.14****	0.07

AChR+ve MG: acetylcholine receptor antibody-positive myasthenia gravis; MuSK+ve MG: MuSK antibody-positive myasthenia gravis; RNST: repetitive nerve stimulation test. [#]p1: P value on comparison between patients with MuSK+ve MG with patients with AChR+ve MG and patients with double-seronegative MG. ^{##}p2: P value on comparison between patients with MuSK+ve MG and patients with AChR+ve MG. *Two-group comparison of MuSK+ve MG and AChR+ve MG, $P=0.02$. **Two-group comparison of MuSK+ve MG and AChR+ve MG, $P=0.09$. ***Two-group comparison of MuSK+ve MG and AChR+ve MG, $P=0.08$. ****Two-group comparison of MuSK+ve MG and AChR+ve MG, $P=0.04$

Table 2: Clinical comparison of treatment with AChEI and steroids between MuSK+ve MG group, AChR+ve MG group, and double-seronegative group

	MuSK-positive MG	AChR-positive MG	Double-seronegative MG	P
First treatment				
Only AChEI, n (%)	3/19 (15.8)	32/51 (62.8)	4/7 (57.1)	
AChEI and steroids, n (%)	16/19 (84.2)	19/51 (37.2)	3/7 (42.9)	0.002*
Patients (%) with good response (>50%) to AChEI	14/19 (73.7)	46/52 (88.5)	5/7 (71.4)	0.19
Patients (%) who underwent thymectomy	3/18 (16.7)	22/51 (43.1)	1/7 (14.3)	0.07**
AChEI				
Max dose of AChEI used, mean (SD)	320 (136.3)	393.2 (170.5)	281.3 (100.1)	0.07
Time from start to max dose (months), median (range)	8 (3-168)	13.5 (1-480)	11 (0.3-144)	0.45
Patients (%) stable on low dose (\leq 120 mg)	6/19 (31.6)	21/51 (41.2)	3/8 (37.5)	0.87
Patients (%) who report adverse effects	5/19 (26.3)	14/51 (27.5)	1/8 (12.5)	0.79
Fasciculations	3	6	0	
Diarrhea	4	5	0	
Abd cramp	1	0	0	
Excessive oral secretions	0	4	1	
Steroid				
No. of patients	20	46	7	
Duration of steroids (months)	24 (1-210)	12 (0.5-228)	3 (1-18)	0.05***
Proportion of time of follow-up pt was on steroids	0.5 (0.07-1)	0.43 (0.01-0.95)	0.63 (0.01-1)	0.09****
Max dose of steroid used (mg), mean (SD)	41.0 (13.8)	37.0 (17.7)	41.4 (18.6)	0.60
Patients (%) who report A/E to steroids	13/20 (65)	24/46 (52.2)	5/7 (71.4)	0.63
Patients (%) who achieved low-dose maintenance dose	9/20 (45)	25/44 (56.8)	5/7 (71.4)	0.45

AChEI: acetylcholine-esterase inhibitor; AChR+ve MG: acetylcholine receptor antibody-positive myasthenia gravis; A/E: adverse effects; MuSK+ve MG: MuSK antibody-positive myasthenia gravis; SD: standard deviation. *Two-group comparison of MuSK+ve MG and AChR+ve MG, $P < 0.0005$; comparison between MuSK+ve MG and DN-MG, $P = 0.34$. **Two-group comparison of MuSK+ve MG and AChR+ve MG, $P = 0.04$. ***Two-group comparison of MuSK+ve MG and AChR+ve MG, $P = 0.67$; comparison between MuSK+ve MG and DN-MG, $P = 0.02$. ****Two-group comparison of MuSK+ve MG and AChR+ve MG, $P = 0.44$; comparison between MuSK+ve MG and DN-MG, $P = 0.04$

out of six AChR+ve MG had generalized MG. All but one patient (AChR+ve) had received multiple immunosuppressant drugs prior to initiation of rituximab.

Out of 32 patients who received 47 courses of IVIg (11 MuSK+ve MG, 19 AChR+ve MG, and 2 DN-MG) [Table 3], all the MuSK+ve MG and 15 out of 19 AChR+ve MG had good response to IVIg. Similarly, out of 28 patients who received 42 courses of PLEX (8 MuSK+ve MG, 20 AChR+ve MG) [Table 3], all the MuSK+ve MG and 15 out of 20 AChR+ve MG had good response to PLEX. There was no significant difference between the groups in terms of incidence of adverse effects.

A larger proportion of AChR+ve MG (43.1%) underwent thymectomy compared with MuSK+ve MG (16.7%) ($P = 0.04$). Out of the three MuSK+ve MG who underwent thymectomy, one had a thymoma and the other two were operated prior to 2000 (before routine testing of MuSK was started).

MuSK+ve MG had a nonsignificant increase in odds of developing severe disease [adjusted odds ratio (OR) 1.27, confidence interval (CI) 0.72–2.24, $P = 0.41$] or poor outcome (adjusted OR 1.93, CI 0.69–5.42, $P = 0.70$) after adjusting for age, sex, age of onset, duration of follow-up, and thymectomy compared with AChR+ve MG.

The MG-QOL15r score was compared between the three groups and there was no significant difference ($P = 0.57$) [Table 4].

DISCUSSION

This study did not find any significant difference between the three groups in terms of clinical symptoms and response to treatment. The long-term outcome (median duration of disease of 3.5–4.0 years) was also similar in all three groups. Interestingly, in previous studies also the long-term outcomes of MuSK+ve MG were similar to AChR+ve MG.^[5-8] In spite of this, the general notion among neurologists is that patients with MuSK+ve MG have grave prognosis.

Over the past two decades, much highlight has been placed on MuSK+ve MG with grave course of disease and patients with benign course of disease are seldom reported.^[9] In our series, three patients never worsened beyond MGFA II. Gungor-Tuncer *et al.* analyzed the factors associated with benign course of disease in MuSK+ve MG ($n = 46$) and deduced that excellent response to corticosteroids in the first 3 months is a predictor for favorable outcome.^[10]

In this study, a significantly larger proportion of patients with MuSK+ve MG (84.2%) were prescribed steroids from the beginning along with AChEI. This reflects the current trend in managing patients with MuSK more aggressively from initial treatment period, anticipating an aggressive course. Empirical initiation of steroids from the beginning leads to higher probability of adverse effects and the risk-benefit analysis of the same requires further evaluation. The

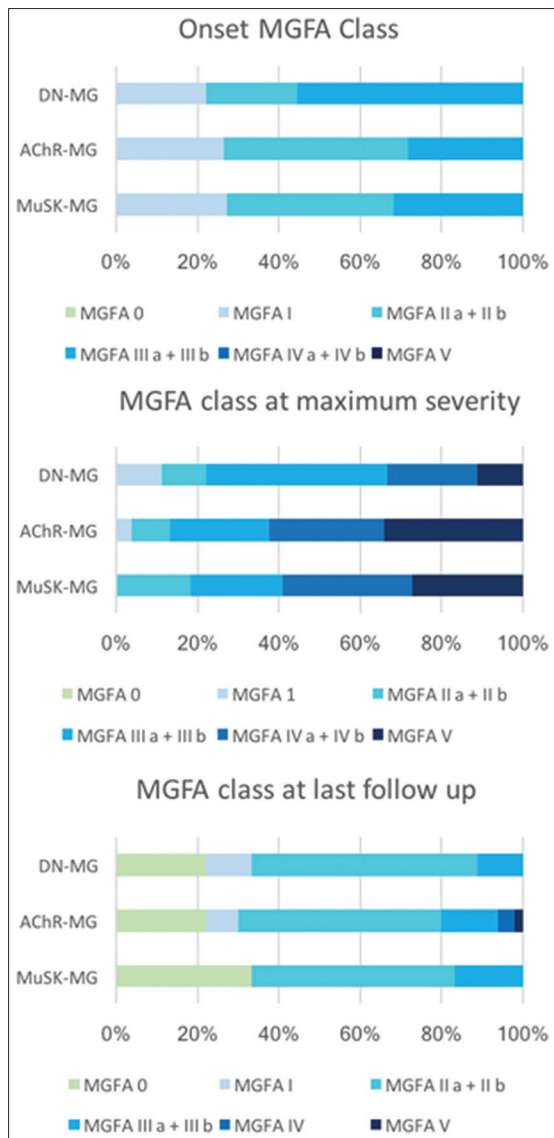


Figure 1: Comparison of MGFA class at onset, maximum severity, and at last follow-up. Onset MGFA $P = 0.59$, max MGFA $P = 0.63$, last follow-up MGFA $P = 0.91$ AChR-MG: acetylcholine receptor-positive antibody myasthenia gravis; DN-MG: double-seronegative myasthenia gravis; MGFA: Myasthenia Gravis Foundation of America; MuSK-MG: muscle-specific kinase myasthenia gravis

treatment outcome between the groups was not significantly different, with equal proportion of patients achieving low maintenance dose of AChEI or steroids in each group. Also, the maximum dose of steroid and the proportion of time each patient was on steroids to the entire duration of follow-up in patients with MuSK+ve MG were similar to patients with AChR+ve MG.

No previous study has compared the response of conventional immunosuppression in MuSK+ve MG group with AChR+ve group. In this study (median duration of follow-up of 3.5–4.0 years), the response to treatment and adverse effects of azathioprine and mycophenolate mofetil (MMF) in MuSK+ve MG were similar to AChR+ve MG.

The current practice in most centers is to avoid thymectomy in non-thymoma MuSK-MG patients. In this study, apart from the single patient with MuSK-MG with thymoma and two other who were operated prior to 2000, none of the other patients with MuSK-MG underwent thymectomy.

A recent study by Tandan *et al.* analyzed the utility of rituximab in myasthenia and showed that MuSK+ve MG had a more robust response to rituximab compared with patients with AChR+ve MG.^[11] Hehir *et al.* provided Class IV evidence in favor of rituximab in MuSK+ve MG.^[12] It is noteworthy that in all these studies, the median severity prior to rituximab was MGFA IV and they had failed multiple immunosuppression therapies before rituximab was started. Díaz-Manera *et al.* recommended rituximab as an early therapeutic option after prednisolone.^[3] Whereas we believe that the decision to start rituximab early in the disease is without definitive evidence, debatable, and may result in undue adverse effects.

In view of evidence of similar efficacy of azathioprine and MMF in MuSK+ve MG and AChR+ve MG in our study, MuSK+ve MG can initially be started on conventional immunosuppression and observed closely. The decision to give rituximab should be guided by the severity of symptoms and the course of disease rather than antibody status alone. The international consensus for management of myasthenia gravis also recommends that rituximab should be used in MuSK+ve MG who do not respond adequately to immunosuppression.^[13]

None of the previous studies studied the quality of life of MuSK+ve MG. We found that the self-reported MG-QoL 15r score in MuSK+ve MG was similar to AChR+ve MG and double-seronegative patients.

MuSK+ve MG form a heterogeneous group and the course of disease may vary from patient to patient. While it is necessary to inform the patient about the expected course of disease and the necessity of regular follow-up, undue negative prognostication can affect the patient’s morale, even those with benign course of disease.

CONCLUSION

We compared the clinical features, response to therapy, and long-term prognosis of 23 MuSK+ve myasthenia with 55 AChR+ve MG and 9 DN-MG and did not find any significant difference between them. The study reinforces the fact that seropositivity for antibodies alone should not be used in isolation to guide the management or predict the prognosis of disease. Clinical features and initial response to therapy in addition to antibody status must be taken into account to plan therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Table 3: Clinical comparison of treatment with immunosuppressant drugs between MuSK+ve MG group, AChR+ve MG group, and double seronegative group

	MuSK-positive MG	AChR-positive MG	Double-seronegative MG	P
Azathioprine				
No. of patients on Aza (%)	18	40	5	
Duration of Aza (months)	28 (0.3-204)	18 (0.3-144)	4 (2- 36)	0.30
Proportion of time of follow-up patient was on Aza	0.46 (0.02-1)	0.46 (0.02-1)	0.17 (0.03-0.43)	0.24
Max dose of Aza used (mg), mean (SD)	130.6 (44.2)	132.5 (43.2)	135 (33.5)	0.93
Patients (%) who report adverse effects to Aza	5/18 (27.8)	15/37 (40.5)	0	0.39
Patients (%) who improved (PR or MM or I)	15/18 (83.3)	33/37 (89.2)	3/3 (100)	0.77
MMF				
No. of patients on MMF	4	6	1	
Patients who report adverse effects to MMF	3	1	0	0.21
Patients who improved (PR or MM or I)	4 [†]	5 ^{**}	1 ^{***}	>0.99
Rituximab				
No. of patients on rituximab	2	6	0	
Patients who improved (PR or MM or I)	2 [§]	5 ^{§§}	0	>0.99
IVIg				
No. of patients given IVIg	11	19	2	
Poor response to IVIg	0	4	0	0.43
No. of patients with adverse effects	1	4	0	0.74
PLEX				
No. of patients who underwent PLEX	8	20	0	
Poor response to PLEX	0	5		0.28
No. of patients with adverse effects	2	5		>0.99

AChR+ve MG: acetylcholine receptor antibody–positive myasthenia gravis; Aza: azathioprine, I: Improved; IVIg: intravenous immunoglobulin; MM: minimal manifestation; MuSK+ve MG: MuSK antibody–positive myasthenia gravis; PLEX: plasmapheresis; PR: pharmacologic remission; SD: standard deviation; U: unchanged. [†]All the patients had attained MM. ^{**}Three patients had improved (I) and two had MM. ^{***}Attained PR. [§]Both the patients had attained MM. ^{§§}Two patients improved (I), two attained MM, one attained PR

Table 4: Comparison of outcomes between MuSK+ve MG group, AChR+ve MG group, and double-seronegative group

	MuSK-positive MG	AChR-positive MG	Double-seronegative MG	P
Postintervention status (n)				
CSR	1	1	0	
PR	1	2	1	
Minimal manifestations (MM)				
MM-0	0	0	0	
MM-1	0	1	0	
MM-2	1	11	1	
MM-3	12	17	4	
Improved (I)	0	8	0	
Unchanged (U), worse (W) or Exacerbation (E)	3	5	0	
Died of MG (D of MG)	1	1	0	
Patients (%) with severe ds (MGFA IV or V) during entire course of illness	11/23 (47.8)	32/52 (61.5)	5/9 (55.6)	0.54
Patients (%) with MGC during entire course of illness	9/23 (39.1)	20/52 (38.5)	1/8 (12.5)	0.39
No. of MGC per patient year	0.09	0.08	0.02	>0.99
Patients (%) with poor outcome*	16/19 (84.2)	32/47 (68.1)	4/6 (66.7)	0.45
Patients (%) requiring IVIg on regular basis	0	4	0	0.57
Median MG-QoL 15r (range)	19 (0-25)	13.5 (0-25)	7.5 (4-11)	0.57

AChR+ve MG: acetylcholine receptor antibody–positive myasthenia gravis; MGC: myasthenia gravis crisis; MGFA: Myasthenia Gravis Foundation of America; MG-QoL 15r: revised myasthenia gravis quality-of-life questionnaire; MuSK+ve MG: MuSK antibody–positive myasthenia gravis; CSR: complete stable remission; PR: pharmacologic remission. *Poor outcome was defined as (1) postintervention status: unchanged, worse, exacerbation, death from MG; (2) inability to achieve low maintenance dose of pyridostigmine or steroids; (3) IVIg therapy on a regular basis

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