



Clinical-Immunological Profile of Myasthenia Gravis-A Tertiary Care Centre Experience

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Abstract

Introduction: Myasthenia gravis (MG) is the commonest acquired autoimmune disorder of neuromuscular junction. Acetylcholine receptor antibodies are associated with MG, particularly generalized MG. There is some suggestion that MG in the Asian population may be clinically different from that in Caucasians. There is a paucity of data on the clinical-immunological profile of myasthenia in the Indian population.

Methods: During a period of one year (September 2007 to August 2008), 32 consecutive patients with a diagnosis of MG, presenting to the Neuromuscular clinic, Department of Neurology, at tertiary care referral were recruited for the study. All patients were followed up regularly for a minimum period of 3 years.

Objectives: To correlate the AChR antibody status and titer with clinical features of MG

Conclusion: AChR antibody are seen in high titer in generalized myasthenia than ocular myasthenia. The presence of higher AChR antibody titer is significantly associated with the presence of thymoma.

Keywords: Myasthenia Gravis, Antibodies, diagnosis, Thymoma.

Introduction

Myasthenia gravis (MG) is the commonest acquired autoimmune disorder of neuromuscular junction. It is an antibody-mediated disease. The autoantibodies formed against the Acetylcholine receptor (AChR) on the postsynaptic membrane are T cell dependent. Acetylcholine receptor antibodies are present in sera from 80% to 90% of patients with generalized MG, about 50% from

those with pure ocular MG and in frequently in healthy people ⁽¹⁾. The remaining 10–20% of patients with generalized MG are AChR antibody negative (seronegative MG, SNMG). The serum concentration of AChR antibodies does not correlate with the clinical severity of myasthenia gravis ⁽²⁾. It has been suggested that the severity of weakness in myasthenia gravis depends on the functional activities of the antibodies (in

accelerating degradation or blocking AChRs, their ability to bind complement, etc) and the differences in neuromuscular junctions in different populations. Approximately 10% of MG patients have circulating antibodies to Musk. Other autoantibodies in MG are anti-striated muscle antibodies (StrAbs), anti-titin antibodies, anti-ryanodine receptor (RyR) antibodies.

Studies from China, show female preponderance and high frequency of seronegative MG and ocular MG^(3,4). MG in the Asian population may be clinically different from that in Caucasians^(5,6). There is a paucity of data on the clinical-immunological profile of myasthenia in the Indian population. Hence, we aim to correlate the AChR antibody status and titer with clinical features of MG in this prospective cohort study.

Methods

This was an observational study of consecutive patients with Myasthenia Gravis (MG) recruited during a one period of the year (September 2007 to August 2008) presenting to the Neuromuscular clinic, Department of Neurology, Government Medical College, Trivandrum, Kerala, India. All patients were followed up regularly till August 2011 with a minimum follow-up of 3 years. The diagnosis was based on history, and clinical findings, including bedside fatigability tests. It would be supported by one or more of the following tests like ice pack test, neostigmine test, and repetitive nerve stimulation (RNS) test suggestive of the postsynaptic disease. Patients with onset at birth (Congenital myasthenia), family history (Familial Myasthenia) and RNS suggestive of presynaptic disease were excluded. Special emphasis was given to the duration of the illness, the severity of the disease and treatment received. The severity of the disease was assessed using Osserman and Genkin's staging system⁽⁷⁾ and the patients were divided into different clinical staging at the time of diagnosis. Nicolet Viking Quest system was used for the repetitive nerve stimulation study. A train of 10 supramaximal stimuli, at a rate of 3 per second

was used for stimulation. The responses were recorded from both proximal and distal muscles. The decrement of more than 10% from the first to the fourth compound muscle action potential responses was considered as positive. Post-exercise facilitation and post-exercise exhaustion were studied after one minute of the isometric exercise of the muscle being tested, whenever required. AChR antibody testing was done for all patients using Radioimmunoassay. HRCT of thorax with contrast was done in all patients to detect thymoma. Symptomatic treatment and immunomodulation were given depending on the stage of the disease. Standard therapy was given. Ocular MG received symptomatic treatment with or without oral steroid. Generalized MG received symptomatic treatment with oral steroid and Azathioprine. Rapid immunomodulation was done by IV Immunoglobulin or Plasma exchange (PLEX). Patients who cannot protect the airway or those with vital capacity <1 liter were intubated and intensive care was given. Thymectomy was offered to all patients with thymoma and those with generalized MG seeking medical treatment preferably within one year of onset of illness.

These patients were followed up for three years and the outcome was measured as death, crisis, and remission.

Results

Thirty-two patients were recruited in one year of whom 17 were males, and 15 were females (M: F - 1.13:1). The mean age was 41.16 years (S.D - 12.01) and ages ranged from 18 to 70 years. The mean (SD) age among males was 44.5 years (14.6) and that of the females were 38.5 years (S8.9). Twenty-one patients (65.6%) had generalized MG and 11 patients (34.4%) had ocular MG. Twenty-two (68.8%) of the studied patients were seropositive MG and the rest 10 were seronegative MG. Mean (SD) age of seronegative MG was 26.3(6.54) years, with an equal gender distribution and an equal number of (five each) ocular and generalized MG. (Table 1.) No thymoma was detected among seronegative MG patients. On the

otherhand, seropositive MG had a mean age of onset at 35.6 years, the with a male preponderance (M: F-13:9), and a higher proportion of generalized MG (72.73%).

Among the ocular MG patients, 6 patients (54.5%) were seropositive, whereas 16 patients (76.6%) of generalized MG were seropositive. (Table 2.) The mean (SD) antibody titer was 7.38 (7.04) among generalized MG patients whereas it was 1.67 (1.94) in ocular MG. This difference was statistically significant ($p = 0.002$). (Table 2.)

Thymoma was seen in 4 patients (12.5%) out of the 32 patients. All patients with thymoma had generalized myasthenia. Male to female ratio among those with thymoma was 3:1. The mean age of patients with thymoma was 38 years (7.8), in contrast to 42.28 years (13.6) among patients

without thymoma. The mean AchR antibody titer was 15.4 (6.4) in thymoma patients and 4.8 (5.7) in patients without thymoma. This difference was statistically significant (p value 0.006).

Three patients had hyperthyroidism and two patients had hypothyroidism. The other comorbidities seen were hypertension (3), diabetes (1) and psoriasis (1). One patient had hepatitis B seropositivity and 2 patients developed malignancy, one had limited small cell carcinoma lung and other had a recurrence of carcinoma of buccalmucosa.

Treatment-related complications were observed in 8 patients which included azathioprine-induced hepatitis in one patient, steroid induced diabetes in two patients, hypertension in two patients, avascular necrosis of femur in one patient and recurrent pyoderma in two patients.

Table 1 Clinical characteristics of patients depending on presence or absence of acetylcholine receptor antibody in subjects with MG

	Total	Seronegative	Seropositive	P value
Number of patients	N=32 (100%)	N=10(31.2%)	N=22 (68.8%)	
M:F ratio	1.13 : 1	1.00 : 1	1.44 : 1	0.23(NS)
Mean age(SD)years	38.5(8.9)	41.7(12.5)	35.6(12.1)	0.11 (NS)
Generalised versus Ocular	21(65.6%) 11(34.4%)	5(50%) 5(50%)	16(72.8%) 6(27.27%)	0.2(NS)

Table 2. Differences between generalized and ocular MG

	Generalized MG N=21(65.6%)	Ocular MG N=11(34.4%)	P value
M : F ratio	15 : 6 = 2.5 : 1	7 : 4 = 1.75 : 1	
AChR Ab positivity, n(%)	16 (76.6%)	6 (54.5%)	0.20(NS)
Antibody titre, mean(SD)	7.38(7.04)	1.67(1.94)	0.002
Thymoma	4(19%)	0 (0%)	0.27(NS)

Discussion

The current study shows the difference in clinical features between AChR antibody seropositive and seronegative patients with MG. It also showed that patients with thymoma also were different.

Our observation of slight male preponderance (M: F -1.13:1) is similar to a study from NIMHANS⁽⁸⁾. Females had a younger age of onset (38.5) compared to males (45.5). Thus early-onset MG has predominantly female and late onset MG had male dominance^(9,10).

The seroprevalence of AchR antibody varies from 59 to 93%^(1,11,12). This would depend on the proportion of patients with generalized MG since the seroprevalence is higher in generalized myasthenia than in ocular myasthenia as in the present series⁽⁸⁾

Approximately, 12-17% of patients with generalized MG lack demonstrable serum AChR antibodies, and they are referred to as the seronegative group^(13,14). In our study, seronegative MG had a younger age of onset (26.3 years), equal male to female ratio, and a higher

proportion of ocular MG (50%). In this study, thymoma was not detected among seronegative MG patients. Lindstrom et al. could not find any consistent similarity among seronegative patients⁽¹⁾. Soliven *et al.* did not find any difference in the age of onset, gender, duration of symptoms or frequency of crises between the seropositive and seronegative patients⁽¹⁴⁾. Vincent *et al.* noted that seronegative patients tended to have shorter duration or symptoms restricted to ocular muscles⁽¹³⁾. Sanders *et al.* observed that seronegative patients were having the milder disease⁽¹⁵⁾.

The AChR antibody titer was significantly higher in generalized MG (7.38) compared to ocular MG (1.67) in the current study. Others have shown that ocular MG, in general, has lower AChR antibody levels⁽¹⁶⁻¹⁸⁾. Contrary to some reports⁽¹⁹⁾ there was no significant correlation between the AChR antibody titer and occurrence of the crisis in our study.

In our study, the mean AChR antibody titer was 15.4 in thymoma patients, and 4.8 in patients without thymoma, which was statistically significant ($p = 0.006$). High antibody titers have been reported in patients with thymoma in MG^(1, 12, 18). Patients with thymoma had a younger age at onset (38 years) and a male preponderance (M: F – 3:1) in this cohort. In contrast, existing literature shows that older age is associated with thymoma and thymic atrophy⁽²⁰⁾.

Conclusion

Acetylcholine receptor antibodies are considered to play a pivotal role in the pathogenesis of myasthenia. They are seen in high titer in generalized myasthenia than ocular myasthenia. The presence of higher AChR antibody titers is significantly associated with the presence of thymoma.

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