



Original Article

## Study of Relationship of Serological Marker Level with Severity of Myasthenia Gravis-A Study from Eastern India

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### ABSTRACT

**Background:** Myasthenia gravis (MG) is an autoimmune neuromuscular disorder characterized by muscle weakness and fatigue. This study aimed to analyze the clinical profile, gender distribution, and the correlation between Acetylcholine Receptor (AChR) antibody levels and disease severity.

**Methods:** A prospective observational study was conducted over two years (2018–2020) involving 45 patients diagnosed with acquired MG. Clinical evaluation, Ice Pack tests, Repetitive Nerve Stimulation (RNST), and AChR antibody assays (ELISA) were performed. Severity was graded using the Myasthenia Gravis Foundation of America (MGFA) classification.

**Results:** A male predominance (66.7%) was observed, with a mean age of 36.8 years. Isolated ocular involvement was the most common initial presentation (28.9%). AChR antibody positivity was 62.2% overall, significantly lower in ocular MG (23.07%) compared to generalized MG (78.1%;  $p < 0.01$ ). While titers were significantly higher in generalized cases, there was no linear correlation between antibody levels and clinical severity across MGFA classes II–V.

**Conclusion:** In this cohort, MG was more prevalent in males. Although AChR antibody titers help distinguish ocular from generalized disease, they do not reliably reflect the degree of clinical severity in generalized MG.

**Keywords:** Myasthenia gravis (MG), Acetyl choline Receptor antibody(AChR Antibody), Myasthenia Gravis Foundation of America (MGFA) classification.

### INTRODUCTION

Myasthenia gravis is an autoimmune condition affecting the postsynaptic neuromuscular junction, leading to fluctuating muscle weakness that may involve ocular, bulbar, limb, and respiratory muscle groups.<sup>1</sup> Diagnosis is typically based on clinical evaluation and supported by electrophysiological studies and serological testing.<sup>2</sup> Clinically, myasthenia gravis is broadly categorized into ocular and generalized forms, depending on the extent of muscle involvement. In ocular myasthenia, the weakness is limited to the eyelids and extraocular muscles. In generalized disease, the weakness commonly affects ocular muscles, but it also involves a variable combination of bulbar, limb, and respiratory muscles.

Patients are classified as seropositive when antibodies against acetylcholine receptors (AChR) or muscle-specific kinase (MuSK) are detected. In contrast, individuals lacking these antibodies are termed seronegative. Approximately half of patients with purely ocular involvement test positive, whereas the proportion rises to nearly 90% in generalized cases. MG is a relatively rare disorder, with reported annual incidence ranging from approximately 7 to 23 cases per million, and prevalence estimates between 70 and 320 per million.<sup>3-6</sup> There tends to be a bimodal distribution to the age of onset with a peak in the second and third decades (female predominance) and a peak in the sixth to eighth decade (male predominance).<sup>7</sup> Evaluation primarily relies on clinical history and examination findings, with confirmation supported by antibody testing and electrophysiological techniques such as repetitive nerve stimulation test (RNST) and single-fiber electromyography (SFEMG). The diagnostic sensitivity of these studies varies considerably depending on whether the patient has ocular or generalized disease.

Patients with positive AChR-Ab, MusK-Ab, or LRP4 assays have seropositive myasthenia gravis. Demonstration of these antibodies, possible in approximately 90 percent of patients with generalized disease, provides the laboratory confirmation of myasthenia gravis. In those with purely ocular myasthenia, the sensitivity of AChR-Ab testing is considerably lower, detectable in approximately half of patients<sup>8,9</sup>. The term "seronegative myasthenia gravis," refers to the 6 to 12 percent of patients with myasthenia who have negative standard assays for both AChR antibodies and MuSK antibodies, and rarely LRP4 antibodies.

## MATERIALS AND METHODS

**Study Design:** This was a prospective observational study conducted at the SCB Medical College and Hospital, Cuttack, Odisha from November 2018 to October 2020. Ethical clearance was obtained from the Institutional Ethics Committee.

**Participants:** Consecutive patients diagnosed with acquired autoimmune MG in the outpatient or inpatient neurology departments were enrolled. We excluded patients with other neuromuscular junction disorders (e.g., Lambert-Eaton Myasthenic Syndrome, congenital myasthenic syndromes) or concurrent motor neuron disease.

The cases were diagnosed by typical clinical feature of Myasthenia Gravis supported by relevant investigations like Ice Pack Test, Neostigmine test, RNST(3Hz), Serum AchR antibody, CT Thorax and exclusion of mimics of Myasthenia Gravis. Patients details were put in a prestructured format having data like Age, Sex, Duration of onset of symptoms, Result of ice pack Test (for patients with ocular involvement) Neostigmine test, RNST(3Hz), Serum AchR antibody level, CT Scan of Thorax. Severity on presentation was done according MGFA grading. Each patients were followed up for 6 months.

### Ice Pack Test-

A small ice pack applied to the closed lid for 2 minutes, after which the patient performed an upward gaze to fatigue the muscle. If the eyelid lifts by > 2mm after 2 minutes of cold application, it is considered positive.

### RNST(Repetitive Nerve Stimulation Test)

RNST done using Salus 2C/4C machine (RMS, India). Stimulation using 3Hz done for both facial and ulnar innervated muscles. Decrement of more than 10% was considered positive.

### Acetyl Choline Receptor Antibody (AChR Antibody)

Serum sample for study for binding Acetylcholine receptor (AChR) antibody done by Enzyme Immunosorbent Assay and value > 0.04nmol/L was considered positive.

### Myasthenia Gravis Foundation of America(MGFA) Grading-

There are five main classes and other subclasses according to the Myasthenia Gravis Foundation of America (MGFA) clinical classification<sup>10</sup>.

- Class I: Any ocular muscle weakness while other muscle strength is normal.
- Class II: Mild weakness affecting muscles other than ocular muscles.
- Class III: Moderate weakness affecting muscles other than ocular muscles.
- Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
- Class II to IV are divided into two subtypes 1. Subtype a. Mainly affecting limb, axial muscles, or both and 2. Subtype b. Mainly affecting oropharyngeal, respiratory muscles, or both.
- Class V: Intubated patients, with or without mechanical ventilation.

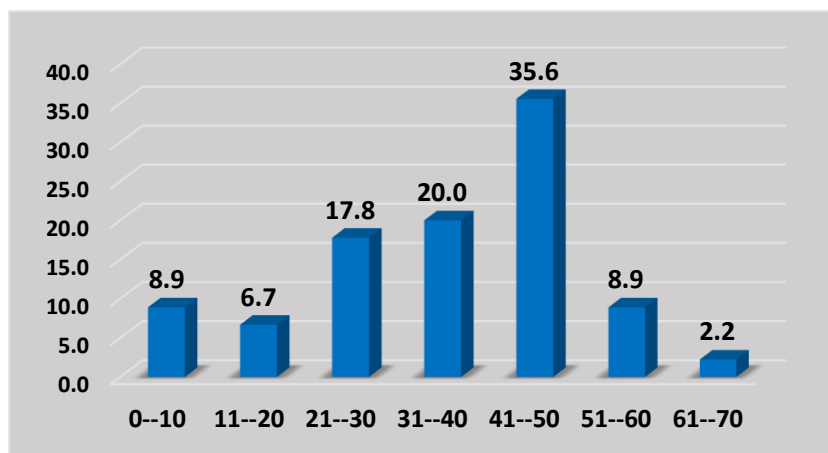
The mean AChR antibody level between different grades of Myasthenia gravis (MGFA Grade I-V) were compared. The mean AChR antibody level was also compared between patients of isolated ocular presentation versus those of generalised presentation to find out whether any correlation exists between Acetylcholine receptor level with severity of presentation.

### Statics

This prospective observational study was done among total 45 number of patients. The study was paired design and non-normal distribution. Categorical variables were summarized using percentages and the continuous were summarized using descriptive statistics. SPSS Statistical software (version 22.0) was used for all the analyses. A Probability value <0.01 was considered statistically significant.

## RESULTS

Total 45 patients with acquired MG were included, out of which 30(66.7%) were male and 15(33.3%) were female. Majority of cases belonged to the age group 41-50 yr. The youngest patient was 7 year of age while the eldest was 65-year-old.



**Graph-1: Group wise age distribution**

**Table 1 GENDER DISTRIBUTION**

Gender	Number	%
Male	30	66.7
Female	15	33.3

Isolated ocular involvement was most common initial presentation in 28.9% subjects while bulbar weakness was least common presentation (2.2%). Ocular finding as one of manifestation was found in 71.1% of patients.

**Table-2 initial Presentation**

Initial Presentation	Number	%	S.D.
Bulbar weakness	1	2.2	0
Limb weakness	3	6.7	9.03
Crisis	3	6.7	8.47
Ocular	13	28.9	9.11
Bulbar+limb weakness	6	13.3	9.1
Ocular+bulbar	10	22.2	9.11
Ocular+limb weakness	9	20.0	10.5
Total	45	100	

AchR antibody was found positive in 62.2% cases. In patient who had presented with isolated ocular feature AchR antibody was positive in 23.07% in contrast to 78.1% in those presented with feature of generalised MG. Anti Musk Antibody was tested in two patients and came negative both the sample.

**Table-3 Serological Profile**

	Number(s)	%	Ocular	Generalised
<b>AchR Antibody (Positive)</b>	28	62.2	3/13, (23.07%)	25/32 ,(78.12%)
<b>AchR Antibody (Negative)</b>	17	37.8	10/13, (76.92%)	7/32, (21.8%)
<b>Anti Musk Antibody (Positive)</b>	0			
<b>Anti Musk Antibody (Negative)</b>	2	100		

Patients presenting with isolated ocular features demonstrated lower mean AChR antibody levels compared to those with generalized disease. This is significant with p value <0.01.

**Table-4 -Comparison of Mean AChR antibody level**

Initial Presentation	Number	%	Mean AChR antibody Level	S.D.
Ocular	13	28.89	2.44	9.11
Generalised	32	71.11	11.35	9.42

**Table-5 Mean AchR level in different MGFA Classes of Patients**

MGFA Class	Mean AchR Level	S.D.
I	2.44	4.18
IIa	17.95	6.25
IIb	4.32	4.77
III	5.9	0
IIIa	10.32	11.88
IIIb	14.18	5.84
IVb	14.56	13.09
V	13.7	9.72

Mean AchR antibody level was maximum in MGFA Class IIa and minimum in MGFA Class I. Although the minimum level of AchR antibody was found in those presented with ocular manifestation, there was no correlation between the level of AchR antibody with severity of class among those having features of generalised myasthenia gravis.

## DISCUSSION

In the present study, the highest proportion of patients belonged to the 41–50-year age group, followed by those aged 31–40 and 21–30 years, while the lowest representation was seen in the 61–70-year group. The mean age at presentation was  $36.8 \pm 14.5$  years. These findings are comparable to those reported by Roy A et al. and Sharma S et al., who documented mean ages of 39 and 40.5 years, respectively.<sup>11, 12</sup> However, a higher mean age of onset (48 years) has been reported by B.S. Singhal et al., indicating some variability across populations.

Female outnumbered male in only in 11-20-year age category. A male predominance (2:1) was observed, consistent with reports by Roy A et al. and B.S. Singhal et al., both of whom documented similar gender distributions. Wing Lok et al., in their hospital-based study from Singapore noted myasthenia to be four times more common in Indian males than females although in their ethnic Chinese and Malay patients there is a female preponderance.<sup>13</sup> Grob D et al., have demonstrated a female predominance, particularly in younger age groups.<sup>15</sup> In the present study, female predominance was observed only in the 11–20-year age category. The observed male predominance cannot be fully explained by general population demographics and may reflect regional or referral biases.

Ocular involvement was the most frequent initial presentation, identified in 28.9% of patients. This is consistent with previous reports, including those by Mantegazza<sup>14</sup> and B.S. Singhal et al., who documented similar proportions of ocular onset. Additionally, ocular manifestations as part of the clinical spectrum were present in 71.1% of patients, which is in agreement with earlier study Oosterhuis HJ et al.<sup>15</sup>

Regarding disease severity, patients were distributed across MGFA classes, with a notable proportion in Classes I and III. The proportion of patients in Class V (6.6%) was higher than that reported by B.S. Singhal et al., but comparable to findings from Roy A et al., suggesting variability in disease severity at presentation across different study populations.

AChR antibody positivity was observed in 62.2% of patients, which is comparable to findings by Bindu P.S. et al. but lower than the 84.7% positivity reported by B.S. Singhal et al. This discrepancy may be attributed to differences in assay sensitivity or patient selection. Among patients with isolated ocular manifestations, antibody positivity was relatively low (23.07%), consistent with previous studies indicating reduced sensitivity of AChR antibody testing in ocular myasthenia. However, this was of lower compared to study of Evoli A et al.<sup>16</sup> A higher positivity rate (78.1%) was observed in patients with generalized disease, in agreement with studies by Vincent A et al. and Chan KH et al.<sup>17, 18</sup>

The mean AChR antibody level was significantly lower in patients with isolated ocular involvement compared to those with generalized disease. However, antibody levels did not demonstrate a consistent relationship with disease severity. For instance, lower antibody levels were observed in some patients with myasthenic crisis compared to those with less severe generalized symptoms. Additionally, no clear trend was identified across MGFA classes, with the highest levels seen in Class IIa rather than in more severe categories. These findings are consistent with previous observations by Sanders DB et al.<sup>19</sup> suggesting that antibody titers may not reliably reflect clinical severity.

## CONCLUSIONS

Although myasthenia gravis is generally reported to be more prevalent in females, a male predominance was observed in the present study. Ocular involvement emerged as the most common clinical presentation.

AChR antibody levels were significantly lower in patients with isolated ocular myasthenia compared to those with generalized disease, indicating a possible role as a marker for disease progression. However, antibody levels did not correlate consistently with disease severity across MGFA classes. Therefore, while AChR antibody titers may provide supportive diagnostic and prognostic information, they should not be considered a reliable indicator of disease severity in generalized myasthenia gravis.

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