Original Research Article

Clinical study of immunological and electrophysiological profile of patients with myasthenia gravis at a super-speciality hospital

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Abstract

Background: Myasthenia gravis (MG) is an autoimmune disorder in which antibodies bind to acetylcholine receptors or related molecules in the postsynaptic membrane at the neuromuscular junction. The diagnosis of myasthenia gravis is confirmed by the combination of history and physical signs and a positive test for specific autoantibodies with supportive evidence of electrophysiological studies. Present study was aimed to study immunological and electrophysiological profile of patients with myasthenia gravis at a superspeciality hospital. **Material and Methods:** The present study was single-center, prospective observational study, conducted in patients >18 years of age, either gender with Diagnosis of myasthenia gravis. **Results:** A total of 77 Myasthenia patients from 26-86 years of age were observed during the study. Mean age of study population was 54.8 years. 48 (62.3%) are males and females contribute 29 (37.7%) patients. Ocular onset presentation was noted in 68 (88.3%) patients. Most common clinical feature was Ptosis (96.1%), dysphagia (49.3%) and diplopia (44.1%). AChR positive was observed in 70(90.9%), MuSK positive was observed in 2 (2.6%) patients. Myasthenic Crisis was observed in 15(19.5%) patients, most common cause of crisis was Infection in 6(40%). 2 (13.3%) patients of myasthenia crisis were managed with non-invasive mode of ventilation and rest of patients required invasive mode of ventilation. Among the patients with myasthenic crisis 14(93.7%) of them recovered and One mortality was noted. **Conclusion:** Most common mode of onset of presentation was ocular, most common clinical feature was ptosis in our study. AChR antibodies were positive in nearly 91% of the patients in our study. RNS was positive in 84% of the patients.
Keywords: myasthenia gravis, ptosis, AChR antibodies, thymoma

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Received Date: 21/11/2021 Revised Date: 10/12/2021 Accepted Date: 12/01/2022

Access this article online	
Quick Response Code:	Website: www.medpulse.in
	DOI: https://doi.org/10.26611/10212136

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder in which antibodies bind to acetylcholine receptors or related molecules in the postsynaptic membrane at the neuromuscular junction. The antibodies induce weakness of skeletal muscles, which is the sole disease manifestation of MG.[1,2,3] With an annual incidence of 8 to 10 cases per 1 million people and with a prevalence of 150 to 250 cases per 1 million.[4] Myasthenia gravis is the major diseases that affect the neuromuscular junction. The Lambert– Eaton myasthenic syndrome and neuromyotonia are other rare NMJ disorders which are presynaptic autoantibody disorders characterized by skeletal-muscle dysfunction.[5] Congenital myasthenic syndromes and toxin-induced conditions (e.g., botulism) can also affect the neuromuscular junction and leads to muscle weakness. The diagnosis of myasthenia gravis is confirmed by the combination of history and physical signs and a positive test for specific autoantibodies with supportive evidence of electrophysiological studies.[6] The primary goals of the

How to cite this article: Praveen Chowdary Meduri, Annam Jaya Madhavi, Susmitha Yella. Clinical study of immunological and electrophysiological profile of patients with myasthenia gravis at a super-speciality hospital. *MedPulse International Journal of Medicine.* March 2022; 21(3): 65-69. https://www.medpulse.in/Medicine/

treatment of patients with MG is to improve symptoms and to prevent generalization in case of focal onset of MG. First-line symptomatic treatment is with acetylcholinesterase (AChE) inhibitors, with pyridostigmine being the most widely used drug.[7] AChE inhibitors alone are frequently insufficient, and oral corticosteroids are required in most cases to improve the symptoms. Steroid-sparing drugs, such as azathioprine, Mycophenolate mofetil, cyclosporine and methotrexate are also treatment options to alleviate the symptoms and/or reduce corticosteroids use.[8] Present study was aimed to study immunological and electrophysiological profile of patients with myasthenia gravis at a superspeciality hospital.

MATERIAL AND METHODS

The present study was single-center, prospective observational study, conducted at Department of Neurology, Sri Ramachandra Medical College And Research Institute, Chennai. **Study duration was** of 2 years (January 2017 to December 2018)

INCLUSION CRITERIA: Patients >18 years of age, either gender with Diagnosis of myasthenia gravis.

EXCLUSION CRITERIA: Patients with less than 18 yrs. of age. Patients with congenital, steroid and inflammatory myopathies and stroke. Patients with history of exposure to toxins like botulin, organophosphates, black widow spider venom and snake venom. Patients not willing to be included in the study

Once identified as a study participant, based on the inclusion and exclusion criteria, a detailed history of every patient was taken after obtaining a written consent. They were then subjected to a detailed clinical examination and the observations were carefully noted. Then Classified into subgroups of Myasthenia and then subjected into AChR Antibodies by RIA if negative then subjected to MuSK Antibodies. Repetitive nerve stimulation is done in Orbicularis Oculi, Nasalis, Abductor pollicis brevis, Abductor digiti minimi where 10% decremental response is considered diagnosis and less than !0% is normal. CT Thorax is done for Thymoma. Outcome measures that were noted for patients were patients with Subgroups of MG, clinical and Electrophysiological profile of patients, clinical profile of patients with Myasthenic crisis and outcome of patients. The analysis was done using Microsoft Office Excel 2013. Statistical analysis was done using descriptive statistics. The quantitative data was represented as their mean ± SD. Categorical and nominal data is expressed in proportions and percentage.

RESULTS

A total of 77 Myasthenia patients from 26-86 years of age were observed during the study. Mean age of study population was 54.8 years. Mean age of males was 61.6 years. Mean age of females was 43.6 years. Out of 77 patients, 48 (62.3%) are males and females contribute 29 (37.7%) patients.

Table 1: Age and gender distribution

Age in years	Male	Female
21- 30	2(2.60 %)	3 (3.90 %)
31- 40	0.00	14 (18.18 %)
41- 50	7 (9.09 %)	4 (5.19 %)
51- 60	9 (11.69 %)	4 (5.19 %)
61- 70	20 (25.97 %)	3 (3.90 %)
> 70	10 (12.99 %)	1 (1.30 %)
TOTAL	**48 (62.3%)**	**29 (37.7%)**

Out of 77 patients, Ocular onset presentation is present in 68 (88.3%), Bulbar onset of presentation is present in 7 (9.1%) and Limb onset of presentation in 2 (2.6%) patients. Out of 77 patients, most common clinical feature was Ptosis present in 74(96.1%). Dysphagia was observed in 38 (49.3%), Diplopia was observed in 30(39%), weakness was observed in 34 (44.1%) and Dyspnoea was observed in 15(19.4%) patients. Out of 74 patients with Ptosis, 54 patients had unilateral ptosis and 30 had bilateral ptosis. Out of 77 patients, AChR positive was observed in 70(90.9%), MuSK positive was observed in 2 (2.6%) and both Antibodies are negative in 5(6.5%). In our study, RNS showed Decremental Response was observed in 65(84.4%) and No decremental Response in 12 (15.6%) patients.

In our study, Thymoma was observed in 5(6.4%), Thymic Hyperplasia was observed in 6(7.7%), Lipoma was observed in 1(1.2%) and Normal in 65 (84.4%) was observed in our study. Out of 5 patients with Thymoma, 2 patients underwent Thymectomy.

Table 2: Clinical, radiological and immunological features

Clinical, radiological and immunological features	No. Of Patients	Percentage
Onset of Presentation		
Ocular onset	68	88.3 %
Bulbar onset	7	9.1 %
Limb onset	2	2.6 %
Clinical Features-		
Ptosis	74	96.1 %
Unilateral	54	
Bilateral	30	
Dysphagia	38	49.3 %
Diplopia	30	39 %
weakness	34	44.1 %
Dyspnoea	15	19.4 %
Serology		%
AChR positive	70	90.9 %
MuSK positive	2	2.6 %
Repetitive Nerve Stimulation (RNS)		
Decremental Response	65	84.4 %
CT Thorax		
Normal	65	84.4 %
Thymic Hyperplasia	6	7.7 %
Thymoma	5	6.4 %
Lipoma	1	1.2 %

In our study, Myasthenic Crisis was observed in 15(19.5%) patients, 2(13.3%) patients have presented as myasthenic Crisis who later diagnosed as myasthenia. In our study, most common cause of crisis was Infection in 6(40%). High dose steroid, Non-Compliance and Unknown cause are found in 2(13.3%) patients. Post-Thymectomy, Hypokalaemia and Drug induced are found in 1 (6.66%) patients.

Table 3: Myasthenia crisis

Myasthenia crisis	No. Of Patients	Percentage
Myasthenic Crisis	15	19.5 %
Onset OF Crisis Related to Diagnosis	2	13.3 %
Cause of Crisis-		
Infection	6	40 %
High dose steroid	2	13.3 %
Non Compliance	2	13.3 %
Unknown cause	2	13.3 %
Post-Thymectomy	1	6.66 %
Hypokalaemia	1	6.66 %
Drug induced	1	6.66 %

In our study, 2 (13.3%) patients of myasthenia crisis were managed with non-invasive mode of ventilation and rest of patients required invasive mode of ventilation. There are 3 patients who required prolonged ventilation who underwent Tracheostomy. In our study, 13 (86.66) patients have received IV Immunoglobulin, Plasmapheresis and Both IVIg and Plasmapheresis were given in 1 (6.66%) patient each respectively. In our study, Cardiac and Urosepsis complications were noted in 2(13.22%) patients each in crisis patients. Cardiac complications- 1 had AF and 1 patient had stress Cardiomyopathy. VAP was noted as complication in 3(20%) patients. Bacteraemia was noted in 3 patients. Among the patients with myasthenic crisis 14(93.7%) of them recovered and One mortality was noted. Out of 77 patients, 26 patients are on Pyridostigmine alone, 3 patients are on pyridostigmine + steroids + Mycophenolate and 47 patients are on Pyridostigmine + steroids + Azathioprine

Table 4: Management, complications and outcome

	No. Of Patients	Percentage
Myasthenic Crisis	15	19.5 %
Non-invasive ventilation	2	13.3 %
Invasive ventilation	13	86.66 %
Treatment of Crisis		
IV Immunoglobulin	13	86.66 %

Plasmapheresis	1	6.66 %
IV Immunoglobulin + Plasmapheresis	1	6.66 %
Complications		
Cardiac		
AF	1	6.66 %
stress Cardiomyopathy	1	6.66 %
Urosepsis	2	13.3 %
VAP	3	20 %
Bactereamia	3	20 %
Outcome		
Recovered	14	93.3 %
Mortality	1	6.66 %
Treatment of Myasthenia Gravis		
Pyridostigmine + steroids + Azathioprine	47	61.04 %
Pyridostigmine	27	35.06 %
pyridostigmine + steroids + Mycophenolate	3	3.90 %

DISCUSSION

Myasthenia gravis presentation can be at any age from infancy to very old age. Epidemiological studies report considerable variability in incidence and prevalence around the world While methodological differences may explain some of this variability, biological and genetic factors may also play a role.[9] Epidemiological studies done so far showed an increasing prevalence over the past 50 years, related to an increase in the frequency of diagnosis in elderly patients, but also likely due to improved ascertainment, reduced mortality rates and an increased longevity of the population. Most of the epidemiology studies are hospital based and there are no many populations-based studies. Reported annual incidence has gradually increased from 1.4-9.1 per million in the1950s-80s to 31-39 until 24.9 per million in 2012. This increasing trend is particularly profound in the elderly due to prolongation of life expectancy. Consequently, over the past six decades, MG prevalence has risen from less than 30 per million to over 300 per million in 2014.[10,11] In present study, myasthenia was seen predominantly among males, comprising of 48 males (62.3%) and 29 females (37.7%). B S Singhal *et al.*,[12] study reported 73% were males and Hamid Suhail *et al.*,[13] has reported around 64.4% were males in his study. But there are studies done by Aline Mansueto *et al.*,[14] and Y Sadri *et al.*,[15] studies who have reported myasthenia was more common in female patients. In B S Singhal *et al.*,[12] mean age of patients was 48 years, with male patients showing mean age of 53 and female patients of 34 years. In Y Sadri *et al.*,[15] mean age is 47.3 years where male is 54.1 and female is 42.3. Our study and the above-mentioned studies have shown a clear trend that myasthenia tends to occur earlier in females compared to males. In our study peak age of onset for males is in 7th decade whereas the peak age of onset for females is in 4th decade. These findings are similar to findings reported by BS Singhal *et al.*,[12] and Y Sadri *et al.*,[15] Onset of presentation in our study, Ocular onset is present in 88.3% patients, Bulbar onset in 9.1% patients and Limb onset in 2.6% patients. According Grob B *et al.*,[16] have more than 2/3rd had ocular presentation, 1/6th patients had Bulbar presentation and 1/10th had limb onset weakness. Our study showed similar results to Rajeev Ojha *et al.*,[17] study with respect to Ptosis, dysphagia, Dysarthria and limb weakness but differs with respect to Diplopia who have reported diplopia is seen among 87% patients. Our study had concurrent results to Y Sadri *et al.*,[15] with respect to Diplopia, Dysarthria and limb weakness but his study has shown lower incidence of ptosis and dysphagia compared to our study. In our study, Serology was found to be AChR positive in 90.9% patients, MuSK positive in 2.6% patients and Both negative in 6.5% patients. This finding is similar to results found in B S Singhal *et al.*,[12] Aline Mansueto *et al.*,[14] and Y Sadri *et al.*,[15] studies. CT Thorax in our study showed presence of Thymoma in 6.5% patients similar to Aline Mansueto *et al.*,[14] and Y Sadri *et al.*,[15] studies. Indian studies like B S Singhal *et al.*,[12] and Suhail Hamid *et al.*,[13] have reported Thymoma in more than 20% patients. In our study Myasthenic Crisis is seen in 19.5% patients which is similar to J M K Murthy *et al.*,[18] study. In our study, first presentation as Myasthenia Crisis before diagnosis of Myasthenia in 13.3% patients. Most common Precipitating factor of Crisis in our study is infection in 40%, High dose of steroids, Non-Compliance and Unknown Cause are 13.3% each, Hypokalemia, Post-Thymectomy and Drug induced are present in 6.66% each patient. As in JMK murthy *et al.*,[18] and S Panda.,[19] study where Infection is most common cause. In our study, Treatment of Crisis is IVIg in 86.66%, Plasmapheresis in 6.66% and Both in 6.66%. In Sudhir Sharma *et al.*,[20] JMK Murthy *et al.*,[18] and S Panda *et al.*,[19] studies where Plasmapheresis is more commonly preferred. Mean duration of ICU stay was 14.5 days and mean duration of hospitalisation was 18 days, similar findings were noted by Sudhir Sharma *et al.*,[20] JMK

Murthy *et al.*,[18] and S Panda *et al.*,[19] In present study, recovery occurred in 93.7% patients which is similar to S Panda *et al.*,[19] which has recovery in 91%. Present study findings differs with Sudhir Sharma *et al.*,[20] study where recovery was 70%. Respiratory infection being common precipitating factor for MC, early institution of antibiotic therapy and Prophylactic vaccination were recommended in patients with MG. Multi-Disciplinary approach such as symptomatic, immuneactive and supportive approaches to therapy have a very good effect on muscle strength, functional abilities, quality of life, and survival. Therapy should be aimed at full or nearly full pharmacologic remission.

Limitations of present study were small sample size, patients underwent a single clinical assessment and there is no long term follow up, newer antibodies or thymic antibodies were not tested and thymectomy was not done in normal or atrophied thymus in our study. We recommend larger, population-based studies for further knowledge of myasthenia gravis.

CONCLUSION

There was a single peak of age at onset in both males and females: in males in the seventh decade and in females in the fourth decade. Most common mode of onset of presentation is ocular onset. Most common clinical feature is ptosis in our study. AChR antibodies were positive in nearly 91% of the patients in our study. RNS was positive in 84% of the patients. It is prudent to exercise great care while withdrawing or introduction of steroids. Similar care is also necessary while introducing steroids in patients with MG.

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Source of Support: None Declared
Conflict of Interest: None Declared