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CLINICAL PRESENTATION, EVALUATION, AND MANAGEMENT OF PATIENTS WITH MYASTHENIA GRAVIS AT A TERTIARY CARE CENTER IN PAKISTAN

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ABSTRACT

Background and objectives:

Little is known about the clinical profile and outcome of myasthenia gravis in Pakistan. The objective of this study is to review the clinical characteristics of patients with myasthenia gravis in Pakistan, and the outcome of investigations and treatment.

Methods:

The study comprised a retrospective review of charts of patients diagnosed with myasthenia gravis at Aga Khan University Hospital in Karachi, Pakistan, over a period of 16 years from 1987 to 2003. The following features were reviewed: (i) clinical presentation, (ii) investigations especially nerve conduction studies, acetylcholine receptor antibodies, and imaging studies of the thorax, (iii) treatments administered (including thymectomy). Data analysis was done using Excel sheets.

Results:

Of the 83 patients, 51(61.4%) were males, whereas 32 (38.6%) were females. The age range was from 12 to 81 years, mean age of 43.7 years (SD± 18.2). In the 60 years plus group, there were three times as many males as compared to females. Limb weakness was noted in 58 (69.9%), ocular symptoms in 57(68.7%), and oropharyngeal symptoms in 54(65.1%) patients. Three (3.6%) presented in a state of myasthenic crisis. Tensilon test was performed in 34 patients and was positive in 31(91.2%), repetitive nerve conduction studies (RNS) were performed in 37 patients and was positive in 26(70.3%), acetylcholine receptor antibodies were done in 60 patients, and were positive in 55(91.7%). Thymic enlargement was seen in 28 out of 43 patients who underwent CT-Scan/MRI studies of the thorax. Besides pyridostigmine, most patients received immunosuppressive therapy with either steroids or azathioprine or both. The thymectomy was performed in 44 patients.

Conclusion:

The general disease pattern of MG, as noted in our series, appears to follow a similar pattern as noted worldwide. However, this retrospective and hospital-based study has its limitations, and more prospective and epidemiological studies are needed.

Keywords: Myasthenia gravis, Clinical profile, Management.

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INTRODUCTION

Myasthenia Gravis (MG), an acquired immunological disorder, is the most common disorder of neuromuscular transmission. Antibodies targeting specific muscle membrane proteins are universally characterized by fatigable weakness depending on severity variably among patients .[1] Over the years, with improved diagnostic modalities, incidence and prevalence of myasthenia have increased to 3.2 per 100, 000 until recently in the United States.[2] Much has been learned about the pathophysiology of MG over the past 30 years, resulting in a wide range of potentially effective treatments.[3] The clinical profile and pathogenesis of MG have been studied extensively the world over, although insufficient data exists from this part of the world, especially Pakistan. Till the early 1960s, this disorder had a high degree of morbidity and mortality with only symptomatic treatment available. The advances in the understanding of its immunological basis and the new treatment modes have revolutionized its treatment completely and today myasthenia gravis is an almost completely manageable disorder with long-term remissions, although no cure is yet available.[4] Although no definitive cure is available the prognosis is good with treatment. Response to treatment is variable depending on the classification of myasthenia gravis; some respond to just symptomatic treatment while others require immunosuppressive medications and surgery. The choice of immunotherapy depends on the clinician's choice considering patient factors. Nevertheless, randomized trials showing benefit over other immunosuppressant is lacking. New advancements targeting B cell growth factors and complements have paved the way for treating refractory myasthenia gravis.[5] Therefore, antibody-mediated acquired neuromuscular transmission disorder is a lifetime disease with good results. Diagnosis is based on clinical history, examination, serological and neurophysiological testing.

We report our clinical, diagnostic, and therapeutic experience of patients with MG over 16 years.

METHODS

Study design: Retrospective chart review

Place and duration of study: This was a retrospective study performed at The Aga Khan University Hospital, Karachi, and consisted of chart reviews of patients who were admitted with a diagnosis of myasthenia gravis during a 16-year period from 1987 to 2003.

Sample size: A total of 102 medical records fitting the diagnostic criteria of myasthenia gravis were obtained from 1987 to 2003, based on the ICD-9 coding, (nos. 358.0 & 358.1).[6] These included both new as well as established cases of myasthenia gravis. Out of 102 medical records, data was missing for 19 patients. Long-term data for 83 patients was thus available for the study.

Sampling technique: Non-probability consecutive sampling method.

Data collection: A standardized questionnaire was made for the data retrieved along with proper coding. The diagnosis of MG was based on the clinical picture and one more of the following: a positive edrophonium (tensilon) test; detectable antibodies on a radioimmunoassay for acetylcholine receptor binding antibodies (Achr Ab); and an electro-decremental response of more than 10% on repetitive nerve stimulation (RNS) studies. Where possible, a computerized tomographic (CT) Scan/ magnetic resonance imaging (MRI) scan of the thorax was obtained. The clinical features and the results of treatment were reviewed and compared with other studies.

Data analysis: Data analysis was done using Excel sheets, which was sufficient for the current analysis.

Ethical considerations: Being a retrospective analysis study, this did not require any ethical clearance as per the policy of The Aga Khan University Hospital.

RESULTS

Of the 83 medical records analyzed, 51 (61.4%) were males whereas 32 (38.6%) were females. The mean age was 43.7 years, with a standard deviation of 18.2 years. The male to female ratio was 1.6:1. In males 35.3% of patients belonged to the 60 years and above age group whereas the numbers of male and female patients were evenly distributed in the age groups before the 60 years age group. There was a more than threefold increase in the number of males above 60 years. Age and sex-specific data is shown in Figure I.

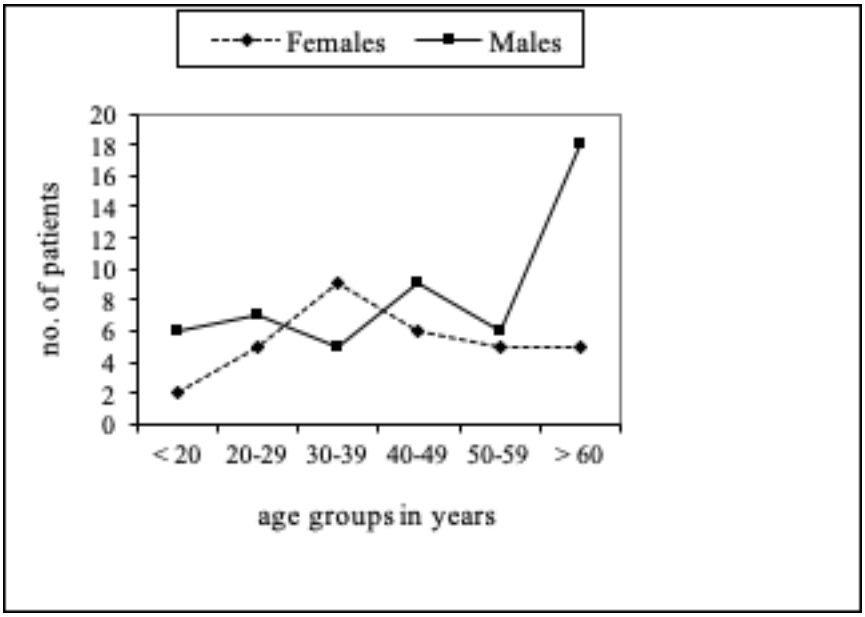

Figure I: Age and Sex-specific data of patients with myasthenia gravis

The main symptoms and signs on the initial visit were broadly categorized as limb weakness, ocular symptoms, and oropharyngeal symptoms. The distribution is shown in Table I.

Table I: Presenting Symptoms of Patients with Myasthenia Gravis
Total patients included in study = 83

Presenting Symptoms	Frequency (%)		
	Males	Females	Total
Limb Weakness	34 (41.0)	24 (28.9)	58 (69.9)
Ocular Symptoms	33 (39.8)	24 (28.9)	57 (68.7)
Oropharyngeal Symptoms	32 (38.6)	22 (26.5)	54 (65.1)
Respiratory Symptoms	10 (12.1)	4 (4.8)	14 (16.9)
Myasthenic Crisis at presentation	3 (3.6)	0	3 (3.6)

Limb weakness, generally mild to moderate was present in 58 (69.9%) patients according to the MGFA classification of Myasthenia Gravis. The involvement was usually bilateral, affecting both the upper and lower limbs with power in the range of 3-4. Ocular symptoms were present in 57 (68.7%) patients. These included ptosis, diplopia, and restricted eye movements that were seen in varying combinations. Oropharyngeal symptoms were present in 54 (65.1%) patients comprising dysphagia, dysarthria, dysphonia, nasal regurgitation, tongue weakness, and weakness in chewing. Apart from the main symptoms, respiratory symptoms like dyspnea, tachypnea, and difficulty in coughing were noted in 14 (16.9%). Three (3.6%) patients presented in a state of myasthenic crisis on their initial visit, necessitating urgent measures including ventilatory assistance, oxygen therapy, etc.

The tests employed to confirm the diagnosis of myasthenia gravis varied from patient to patient depending on the urgency and previous workup. The main investigations included the Tensilon test, repetitive nerve conduction studies, and acetylcholine receptor antibodies. Tensilon test was performed on 34 patients. It was positive in 31 (91.2%), negative in 1 (2.9%) and inconclusive in 2 (5.9%) patients. Similarly repetitive nerve conduction studies were performed in 37 patients, being positive in 26 (70.3%), negative in 10 (27.0%) and inconclusive in 1 (2.7%) patient. Acetylcholine receptor antibodies were done in 60 patients, these being positive in 55 (91.7%) and negative in 5 (8.3%) patients. Investigations to determine the thymus gland on radiology included a Computed Tomography scan and Magnetic Resonance Imaging of the thorax. 43 patients underwent CT scan. It was reported normal in 15 (34.9%) patients and thymic enlargement was reported in 28 (65.1%) patients. MRI was done in only in 4 patients and was reported to be normal in all four cases.

The main drugs that were employed in treating myasthenia gravis included cholinesterase inhibitors, steroids, and azathioprine. It was difficult to assess and analyze their response rates due to the variable pattern of the follow-up reports. All the patients received cholinesterase inhibitors; 44 patients received steroid therapy while 28 patients were treated with azathioprine. In addition to the above-mentioned drugs, out of 83 patients, three were given IVIG therapy and all of them responded well over the first few weeks that they were assessed. The three patients who presented with myasthenia crisis on the initial visit required ventilatory support with a positive outcome. Thymectomy was done in 44 patients. Out of these, 38 procedures were done at this institute while 6 were done elsewhere.

DISCUSSION

Although Myasthenia Gravis is a well-understood disorder, it is not a frequently encountered disease. The reported incidence figures for MG are widely variable, from around 2.5 to 4.5 per million population to 21 per million .[7-9] Similarly, the prevalence rates are reported 45 to 100 per million and to 100 to 150 per million .[1,10] The figures could well be higher because MG appears to be generally under-diagnosed .[3]

Myasthenia can occur at any age. The peak ages of onset of MG in females are between the teens and the thirties, whereas in males, they are between 50 and 70 years of age.[11] In our series, except for the age group between 30-39 years, there were more males as compared to females (Figure I). This contrasts with other reports, where the incidence in females is higher in the younger decades.[11] However, the number of males in the 60-plus age group was significantly more than females (18 v/s 5), which is consistent with the observed increased incidence in males beyond the 5th decade, although the numbers may be small for comment.[9]

In our study, limb weakness was as commonly seen as weakness in the ocular and oropharyngeal muscles. This contrasts with other studies, which show that ocular and oropharyngeal symptoms are the more common initial symptoms.[3,12] This could be explained by the fact that most of our patients usually present for treatment somewhat late in the course of the disease.

The main tests that aid in the confirmation of the diagnosis of MG include pharmacological (Tensilon test), electrophysiological (nerve conduction studies), and immunological (acetylcholine receptor antibodies). The Tensilon test can be positive in over 90% of the patients suffering from myasthenia gravis although it also has a high false positive rate.[3] In our study, the Tensilon test was performed on 34 patients and was positive in 31(91.2%) patients. This test was done in only 1/3 of our patients, because of the possible risk of developing potentially lethal vagal bradycardia, particularly in the elderly as well as due to the high rate of false positivity.[11]

Repetitive nerve stimulation (RNS) studies have a very high sensitivity rate, especially if done on a weak muscle. The sensitivity is around 70-75% and the specificity is around 95%. This yield can be increased up to 90% in extended studies, especially in warm proximal muscles.[13] In our series, 70% of patients showed a positive decremental response to RNS. Similarly, 91.7% of our patients tested positive for acetylcholine receptor antibodies, which is consistent with what is reported in the literature.[11, 14] The concentration of AChR antibody varies widely among patients and therefore it cannot be used to predict the severity of the disease. However normal antibody levels do not exclude diagnosis.[14]

The presence of thymic hyperplasia and thymomas are strongly associated with myasthenia gravis. In our study 43 patients underwent CT scan, out of which thymic enlargement was reported in 28 patients while it was reported to be normal in 15 patients. MRI Scan of the thorax was performed in four patients and was reported as normal in all four. The thymectomy was performed on 44 patients. The benefits of thymectomy are controversial and subject to intense debate in recent years.[15] For this reason, the benefits of thymectomy alone would be difficult to evaluate in a retrospective series like the present one.

The treatment of myasthenia gravis requires initial stabilization with cholinesterase inhibitors, followed by the administration of immunosuppressive agents. Although Thymectomy is generally recommended for all cases of generalized myasthenia gravis, this view is not shared by all.[16] Most of our patients too, were stabilized with the use of appropriate doses of pyridostigmine. Steroids were used in 44 patients, whereas azathioprine was the other immunosuppressive agent of choice, especially for long-term use (28 patients). Long-term follow-up of such patients is desirable; however, this was not possible in our study, due to a very poor rate of follow-up for various reasons.

Although the incidence of myasthenic crisis in patients with myasthenia gravis has remained at 15–20% worldwide over many decades the mortality has declined from 80% in the 1950s to 4% in 1994. [9,11] Claytor B et al. state that US cohorts show mortality of less than five percent in myasthenic crisis patients. Generally, the prognosis is favorable.[17] A German retrospective study published a mortality of around 12% among crisis sufferers. However, this was strongly associated with multiple comorbidities and death due to multiorgan failure.[18] Unfortunately, being an underdeveloped country, scarcity of data exists.

In our series, three patients were presented in a state of myasthenic crisis, and all three were revived successfully with a combination of ventilatory assistance, plasmapheresis, and supportive measures. Also, there were no mortalities directly due to the disease. Though it is a life-threatening condition, prompt and aggressive timely treatment can be the life savior.

The retrospective nature of the study and the fact that this study presents old data are limitations of the study.

CONCLUSION

In summary, our observations on the clinical patterns of MG in Pakistan, the findings on investigations, and its therapeutic responses appear to be generally like those reported in other studies around the world. However, further prospective studies are required to validate this data. We also need epidemiological information to ascertain the exact disease burden in this region.

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Shafaq Saleem; Concept, data analysis, manuscript writing
Salim Allana; Concept, manuscript revision
Rabia Qaiser; Data interpretation, manuscript revision
Rohma Shamsi; Data interpretation, manuscript revision
All the authors approve the final version to be published, and agree to be accountable for all aspects of the work.