Myasthenia Gravis: A Comparison of Clinical Presentation and Diagnostic Tests among different Gender Groups in Pakistani Population

Objective: To study the clinical presentation and diagnostic tests utilized for the confirmation of Myasthenia Gravis (MG) in different gender groups.

Study design: Cross Sectional Study.

Place and Duration of Study: This study was conducted at Fauji Foundation Hospital, Rawalpindi and Pakistan Myasthenic Welfare Organization, Islamabad, from Feb 2008 to Jan 2010

Patients and Methods: A total of 64 patient having at least one diagnostic test positive for MG, were selected on purposive, non probability group basis, All those were excluded that lack pharmacological response, laboratory or electro-diagnostic result, in favor of MG. Comparison was made between two groups (male and female). Different diagnostic modalities utilized for the confirmation of MG were analyzed.

Results: There were 32 patients in each group. Mean age at onset of MG was 24.78 ± 9.09 and 33.56 ± 12.05 in female and male group respectively (p=0.002). Most of the patients (79.69%) had onset before 40 yrs of age and out of these 58.82% were females. Major clinical presentation includes ocular symptoms in 90.62% & 84.37% followed by easy fatigability in 81.25% & 71.87%, bulbar weakness in 46.87% & 56.25% and proximal limb weakness in 32.25% & 24.19% in female and male patients, respectively. Investigations utilized for confirmation of MG are Anti AChR antibody (87.1%), Repetitive Nerve Stimulation (69.35%) & Neostigmine test (20.97%). Thymic hyperplasia was found in 90% and 22% of thymectomy samples in female and male respectively.

Conclusion: The clinical presentation of MG in both gender were comparable. Most of the patients had onset before 40 yrs of age and thymic hyperplasia was more common in this group. Commonly utilized investigations include AChR antibody, RNS & Neostigmine test.

Key words: Myasthenia gravis, autoimmune disease, thymectomy

Introduction

Myasthenia Gravis (MG) is a neuromuscular disorder manifested by weakness and fatigability of voluntary muscles.\(^1\) It is a model autoimmune disease, with defined antigens and pathogenic auto antibodies.\(^2,3\) The antibodies are either directed against the muscle nicotinic acetylcholine receptors (nAChR) itself or against other post synaptic targets such as the muscle specific kinase (MuSK) that indirectly reduce nAChR numbers.\(^4,5\)

MG can begin at any age, but onset in the first decade is relatively rare (10%). The peak age of onset is between 20 -30 yrs in female and between 50-60 yrs in male.\(^6\) The incidence in female is higher under the age of 40 yrs whereas in later life it is higher in males. The initial symptoms or signs of MG are ptosis or extraocular muscle weakness in up to 65% of patients.\(^6,7\) While increasing muscle fatigue, bulbar and proximal limb weakness occurs in generalized MG. Some patients may present with neuromuscular respiratory failure from the onset.\(^6\)

In addition to history and examination, various modalities are used for the diagnosis of MG including pharmacologic (Tensilon Test), electro diagnostic
(Repetitive Nerve Stimulation & Single Fiber EMG) and immunologic methods (Anti AChR Antibodies & Anti MuSK Antibodies). 8-10

The thymus has been implicated as having a central role in the pathogenesis of MG and thymic abnormalities such as thymic hyperplasia and thymoma are present in a large percentage of MG patients.11 Due to this well known association of MG with thymic abnormalities, imaging (CT scan) of chest for detection of anterior mediastinum mass is also an important prelude especially when thymectomy is considered, in addition to pharmacological treatment both symptomatic and immune modulating. 12, 13, 14

Materials and Methods

This cross sectional study was conducted on 64 patients, selected on non probability, purposive, convenience sampling; with clinical diagnosis of Myasthenia gravis presenting to the Out-patient Department of Neurology, Fauji Foundation Hospital, Rawalpindi and Pakistan Myasthenic Welfare Organization (PMWO), Islamabad, during Feb 2008 to Jan 2010.

The patients of any age group and gender with clinical suspicion of Myasthenia gravis who had at least one diagnostic test (Neostigmine test, Repetitive Nerve Stimulation test, Acetylcholine Receptor Antibodies test) positive for MG were included in this study. All those patients were excluded from the study who lack pharmacological response, laboratory or electrodiagnostic results in favor of MG.

Procedure: Sixty four patients who met the above mentioned criteria were included in this study. An informed consent was obtained from them. There were two groups in this study (male and female) comprising of 32 patients each. The record of patient was evaluated with CT scan chest, for thymic status were evaluated with CT scan chest, for thymic status were noted. Details of different diagnostic modalities utilized for the confirmation of MG were analyzed, including Neostigmine test, Repetitive Nerve stimulation test and anti ACh Receptor Antibody test. Details of patients, evaluated with CT scan chest, for thymic status were collected and thymectomy details were noted.

Statistical package for social sciences (SPSS) version 13.0 was used to analyze the data in terms of inferential statistics. Independent-Samples T test and Logistic regression was used to demonstrate the statistical significance between the two groups (female & male). A ‘p value’ of 0.05 or less was considered statistically significant.

Results

A total of 64 patients were included in this study. There were two groups with equal number of patients. In the female group mean age was 30.59 (range 19-53 yrs) while in male group it was 38.66 (range 17-72 yrs).

Mean age at onset of MG symptoms was 24.78 ± 9.09 (range 13-48 yrs) and 33.56 ± 12.05 (range 14-67 yrs) in female and male group respectively [95% CI 3.49-14.12, p=0.002] Table I. Most of the patients (79.69%) had onset before 40 yrs of age and out of these 58.82% were females.

Table I: Comparison of Age in Female & Male groups

<table>
<thead>
<tr>
<th>No of Patients</th>
<th>Female Group</th>
<th>Male Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>30.59</td>
<td>38.62</td>
<td>34.61</td>
</tr>
<tr>
<td>range</td>
<td>19-53</td>
<td>17-72</td>
<td>17-72</td>
</tr>
<tr>
<td>Age at onset (yrs)¹</td>
<td>24.78</td>
<td>33.56</td>
<td>29.12</td>
</tr>
<tr>
<td>range</td>
<td>13-48</td>
<td>14-67</td>
<td>13-67</td>
</tr>
</tbody>
</table>

¹ (95% CI 3.49-14.12, P=0.002)

Among those who had onset before 40 yrs of age, males were 21 (mean 26.52±6.7 yrs) and females were 30 (mean 23.33±7.32 yrs) [95% CI 0.8-7.18, p=0.114]. Among those who had onset after 40 yrs of age, males were 11 (mean 47±7.6 yrs) and females were two (mean 46.5±2.12 yrs) [95% CI 5.94-6.94, p=0.86]

Among the clinical presentation, ocular symptoms (ptosis and or diplopia) were the most common; these were present in 90.62% of female and 84.37% of male patients. The second common symptom was generalized weakness and easy fatigability in 81.25% females and 71.87% males. Bulbar weakness was present in 46.87% of female and 56.25% of male patients. While 32.25% and 24.19% of patients had proximal upper limb and lower limb weakness respectively. Figure I

Anti AChR Antibody test was done in 87.1% of patients (27 in each group). This titer was positive in 81.48% of female and 70.37% of male patients. The range of titer and mean values are shown in Table III.

As shown in Table II, Repetitive Nerve Stimulation (RNS) test was done in 43 out of 62 patients. This test was positive for MG in 72.22% (13 out of 18) of female and 80% (20 out of 25) of male patients. RNS did not showed any decrement response in 16.67% female and 12% males while it was mildly positive/ inconclusive in 4 patients (two in each group).
Neostigmine test was done in 20.97% of patients (6 females and 7 males). It was positive for MG in all the patients. Table II.

Table II: Comparison of diagnostic tests done in our patients of MG

<table>
<thead>
<tr>
<th></th>
<th>Female Group</th>
<th>Male Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti AChR Ab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>27^2</td>
<td>27^2</td>
<td>54^1</td>
</tr>
<tr>
<td>Positive titer</td>
<td>22 [81.48%]</td>
<td>19 [70.37%]</td>
<td>41 [75.93%]</td>
</tr>
<tr>
<td>Negative titer</td>
<td>5 [18.52%]</td>
<td>8 [29.63%]</td>
<td>13 [24.07%]</td>
</tr>
<tr>
<td>RNS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>25</td>
<td>43</td>
</tr>
<tr>
<td>Positive for MG</td>
<td>13 [72.22%]</td>
<td>20 [80%]</td>
<td>33 [76.74%]</td>
</tr>
<tr>
<td>Normal</td>
<td>3 [16.66%]</td>
<td>3 [12%]</td>
<td>6 [13.95%]</td>
</tr>
<tr>
<td>inconclusive</td>
<td>2 [11.11%]</td>
<td>2 [8%]</td>
<td>4 [9.30%]</td>
</tr>
<tr>
<td>Neostigmine Test done</td>
<td>6</td>
<td>6 [100%]</td>
<td>13 [100%]</td>
</tr>
<tr>
<td>positive</td>
<td>6 [100%]</td>
<td>7 [100%]</td>
<td>13 [100%]</td>
</tr>
</tbody>
</table>

^1 (P=0.57) ^2 (95% CI 17.76-70.68, P=0.23)

Table III: Comparison of AChR Antibodies titer in Female & Male Groups

<table>
<thead>
<tr>
<th></th>
<th>Female Group</th>
<th>Male Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti AChR Ab Positive total Patients</td>
<td>22</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td>mean titer</td>
<td>80.20</td>
<td>53.74</td>
<td>67.94</td>
</tr>
<tr>
<td>range</td>
<td>0.83-380</td>
<td>0.47-129.2</td>
<td>0.47-380</td>
</tr>
<tr>
<td>Low Vs High titer Pt with Low titer (&lt;50)</td>
<td>10</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Pt with high titer (&gt;50)</td>
<td>12</td>
<td>8</td>
<td>20</td>
</tr>
</tbody>
</table>

Discussion

MG is a potentially serious but treatable neuromuscular junction disorder. It affects the female at a relatively younger age. In our study the mean age of onset was 24.78 yrs in females as compared to 33.56 yrs in males, which was statistically significant (p=.002). MG has been known to occur at any age but the gender distribution is such that it is more common in females below 40 yrs of age. Our study showed that 79.69% of the patients had onset before 40 yrs and among these patients 58.82% were females. While among the patients with onset after 40 year of age males outnumber the females (11 Vs 2).

The hallmark of MG is fatiguability. Muscles become progressively weaker during periods of activity and improve after periods of rest. Muscle that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are especially susceptible. The muscle that control breathing and neck and limb movements can also be affected. In our study the most common presentation is with ocular symptoms (90.62% and 84.37% in females and males respectively), which is in accordance with the study reported by Aurangzeb et al, in which the ocular symptoms were present in 91%. Second most common symptom was generalized weakness and fatiguability which was present in 81.25% of female Vs 71.87% of males.
Bulbar weakness was observed more in males as compared to female patients (56.25% Vs 46.87%). The proximal limb weakness was observed more in females than males (32.25% Vs 24.16%).

Three diagnostic modalities were utilized in confirmation of MG. Among these Anti AChR Antibody test, RNS and Neostigmine test were done in 87.1%, 69.35% and 20.97% of patients respectively.

The demonstration of serum anti-AChR Antibody proves the diagnosis of MG. However, their absence does not exclude it because anti-AChR Antibodies are detectable only in 80-90% of generalized MG and 30-50% of ocular MG. In our study anti-AChR Antibody test was done in 87.1% of patients and the test was positive in 81.48% in females as compared to 70.37% in males, while it was negative in 5 and 8 patients in female and male group.

An interesting observation was made while analyzing the titers of anti AChR Antibodies in both groups. It was seen that mean titers were higher (80.2) in female group than in male group (53.74) and the range was also higher in female group (0.83-380 Vs 0.47-129.2). Low titer was seen in 21 patients (10 female & 11 male), while high titer was found in 20 patients (8 female & 12 male).

Muscle fibers of patients with MG are easily fatigued, and thus do not respond as well as muscles in healthy individuals to repeated stimulation. By repeatedly stimulating a muscle with electrical impulses, the fatiguability of the muscle can be measured. RNS was the second common investigation utilized for the confirmation of MG. RNS was positive in 72.22% of female and 80% of male patients. This test has limitations that not only it requires equipment and skill but can still be inconclusive as distal muscle are routinely checked and MG usually affects the proximal muscle. While in patients with ocular MG, the yield of RNS is further decreased.

The tensilon test is infrequently performed to identify MG; its application is limited to the situation when other investigations do not yield a conclusive diagnosis. This test requires the intravenous administration of edrophonium chloride, due to non availability of this drug in our setting, Neostigmine test is performed. These are the drugs that block the breakdown of acetylcholine by cholinesterase, and temporarily increase the levels of acetylcholine at the neuromuscular junction. The patient must have some measurable clinical sign, especially involving the eye muscles and backup of cardiac support in case arrhythmias occurred. This test was performed in 20.97% of patients (6 female and 7 male) and was positive in all.

It is a well known fact that thymic tumors occur in 10-15% of patients with MG and lymphofollicular hyperplasia of the thymic medulla in 65%. The proportion with hyperplasia is even higher in younger patients. CT scan of chest is done to visualize the thymic mass, as in our study it was done in 54.84% of patients (20 females and 14 males). Out of these 40% and 42.85% showed anterior mediastinal mass in both groups respectively.

Out of total thymectomies, thymic hyperplasia was present in 90% & 20% of thymectomy samples in female and male groups respectively. Thus showing that presence of thymic hyperplasia is statically significant (p=0.02) in female group which has earlier age at onset of MG symptoms.

Conclusion

The clinical presentation of MG in both gender were comparable. Most of the patients had onset before 40 yrs of age and thymic hyperplasia was clearly more frequent in female patients with onset at an earlier age. Among the three investigations AChR antibody test was most commonly utilized for the confirmation of MG followed by RNS. Neostigmine test though very effective tool to confirm MG was utilized least, that too in situations where other investigations did not yield a conclusive diagnosis.

References


