MYASTHENIA GRAVIS: EXPERIENCE IN A UNIVERSITY HOSPITAL

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Objectives: Study the clinical profile of patients diagnosed with myasthenia gravis.

Setting: Neurology Services Unit at King Fahd Hospital of the University (KFHU), Al-Khobar, Saudi Arabia.

Subject and Design: Review of all Medical records of patients diagnosed with myasthenia gravis at KFHU between September 1,1991 and August 31, 1995.

Main Outcome and Results: Myasthenia gravis was diagnosed in 35 patients; 27 Saudis (20 females, 7 males), 8 non-Saudis (4 females, 4 males). The annual incidence in Saudis was 1.6/100,000 with a hospital frequency rate of 6.5/100,000. The peak frequency was in the third decade, 73% of all patients were less than 30 years of age. The salient clinical feature of weakness involved the following muscles in order of frequency; appendicular (92.6 %), ocular (81.5%), bulbar (29.6 %) and respiratory (14.8 %). Nine patients (7 females, 2 males mean age 26.6 years) had thymectomy. Clinical response to supplement or immunosuppressive therapy was assessed objectively: 25 patients were fully functional and only 2 patients had residual symptoms.

Interpretation: Myasthenia gravis is not uncommon in Saudis and conforms to the pattern described in other populations.
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Myasthenia Gravis (MG) is an autoimmune disease involving the post-synaptic terminal of the neuromuscular junction and has a heterogeneous clinical presentation[1-3]. The thymus plays a significant role in its pathogenesis as a result of the various immune mediated mechanisms targeted at the nicotinic acetylcholine receptor sites[4-6]. Although MG is uncommon, it occurs in all populations with a wide age distribution[7-12]. The available information on MG in the Saudi Arabia is scarce[13]. We describe the clinical features of MG in Saudis seen in a tertiary care hospital in Saudi Arabia over a five-year period.

METHODS

The records of all patients presenting to the Neurology Clinic of King Fahd Hospital of the University (KFHU), Al-Khobar, Saudi Arabia from September 1, 1991 till August 31, 1995 with weakness, ptosis, bulbar weakness (dysphagia, dysphonia, nasal regurgitation), visual symptoms (diplopia, blurred vision, ptosis) were reviewed. All the patients were seen and managed personally by at least one of the authors, and have been followed up from six months to 4 years.

The diagnosis of MG was accepted on at least three of the criteria: (a) clinical evidence of muscle fatiguability; (b) improvement in weakness (appendicular or bulbar) on intravenous injection of 2-10 mg Edrophonium Hydrochloride (Tensilon); (c) electromyographic evidence of a post-synaptic neuromuscular junction pathology (at least 15 % decrement in compound muscle action potential following repetitive stimulation of the nerve supplying the tested muscle at a low frequency of 2 or 3 Hz either at rest, following exercise or ischemia). The commonly evaluated muscles included the abductor pollicis brevis, abductor digiti minimi, deltoid and orbicularis oculi; (d) elevated levels of acetyl choline receptor (ACh) titres.

Individuals who had been evaluated by other physicians and on regular anticholinesterase medications and/or previous history of thymectomy with adequate documentation from the initial evaluating physician and who were on regular follow up by the Neurology Clinic of KFHU, Al-Khobar were accepted for the study.

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The baseline investigations included complete blood count, erythrocyte sedimentation rate, serum immunoglobulins, various antibody titres (anti-smooth muscle, anti-nuclear, etc), latex serological test, rheumatoid factor, lupus erythromatous (LE) cell test, creatinine kinase (CK), thyroid function tests, transaminases, blood sugar, electrolytes, BUN and pulmonary function tests. Radiological investigations performed were radiographs of the chest, computerized tomograms (CT) and MRI of the chest and mediastinum. Histology of the thymus was obtained when available or indicated. Disease severity was classified as I, IIa, IIb, III and IV[9,14].

Medical treatment was the mainstay of management. The drugs commonly used were anticholinesterases (Pyridostigmine; Neostigmine). Immunosuppression was achieved with steroids (Prednisone, Prednisolone) and/or azathioprine (Imuran). These drugs were used either singly or in combination. Plasmapheresis was an adjunct therapy when practicable and it became readily available in our facility only within the last 3 years. Thymectomy was also performed when indicated or permitted by either the patient or their relatives. Patients whose symptoms persisted even after thymectomy were maintained on drugs. The patients were thereafter classified into group 1 who underwent thymectomy and group 2 who were treated with other modalities without thymectomy.

Response to therapy with/without thymectomy was classified as: (a) excellent when no detectable

Table 1. **Clinical characteristics of Saudi patients with myasthenia gravis (MG)**

Feature	*Thymectomy*		*No Thymectomy*		*Total*	
					No	*%*
Number	9		18		27	100
M	2		5		7	31.0
F	7		13		20	69.0
Age group in years			M	F		
< 30			5	15	20	74.1
30 - 50			1	3	4	14.8
> 50			1	2	3	11.1
Total			7	20	27	100.0
Mean D-Sy*	15.9		23.5			21.0
M	18.4		17.1			
F	15.3		26.3			
Cl-Grade**	M	F	M	F	M	F
I	0	0	0	2	0	2
IIa	1	0	0	6	1	6
IIb	1	5	4	5	5	10
III	0	1	1	0	1	1
IV	0	1	0	0	0	1
Cl-Response***						
Good	2	7	4	12	6	19
Poor	0	0	1	1	1	1

* *Mean D-Sy: Mean duration of symptoms in months*

** *Cl-Grade : Clinical grade*

*** *Cl-Response: Clinical Response*

weakness at rest or after exercise and on no medication; (b) good when the patients were still maintained on medication but fully functional and able to cope with activities of daily living without any difficulty; (c) fair when the patients were able to cope with activities of daily living but requires regular medication at least 6-hourly daily; and (d) poor when the patients showed no clinical improvement in spite of at least 4-hourly medication daily or was worse than initial presentation.

Although elective thymectomy was offered to females who were under 30 years old, individuals with bulbar features and/or severe respiratory symptoms (FEV < 1.5L; FVC < 2.5L; blood gases with significant CO_2 retention, etc) irrespective of the value of the ACh titres and those with demonstrable thymic mass on CT or MRI were offered surgery. The major indication for thymectomy was the poor response to medication.

Statistical Analysis: Means were compared using the Student's t-test for unpaired independent samples and one-way ANOVA for means of more than two subgroups. Fisher's exact test was used to compare discrete data and Mantel Haenszel test of significance used to assess clinical response between subgroups.

RESULTS

During the study period, 35 patients with MG were seen: 27 Saudis (20 females, 7 males), 8 non-Saudis (4 females, 4 males). MG in Saudis had an annual incidence of 0.56/100,000 and a hospital frequency rate of 6.5/100,000.

The clinical characteristics of the 27 Saudi patients are shown in Table 1. Nine (7 females, 2 males; mean age 26.6 years) had thymectomy (Group 1) and 18 (13 females, 5 males; mean age 25.0 years) did not (Group 2). Peak frequency was in the third decade and 74 % of all the patients were < 30 years of age. The overall female to male ratio was 2:1 although it was higher at 3.5:1 for Group 1. The overall duration of symptoms ranged from 1 week to 8 years with a mean of 21 months (16.0 and 23.5 months for Groups 1 and 2 respectively). There was no significant difference between the mean ages or mean duration of symptoms of either males and females or groups 1 and 2 patients respectively ($p > 0.5$). The onset of disease was acute (duration of symptoms < 1 year) in 16 patients (41 %) and there was no significant difference in this pattern of presentation between the two groups (5 of 9 group 1; 7 of 18 group 2).

The clinical grade IIb was the most frequent form of presentation: 6 from group 1 (5 females, 1 male) and 9 from group 2 (4 males, 5 females). The other grades of disease severity were as follows; grade 1: 2 patients (both females from group 2); grade IIa: 7 patients (1 male from group 1, 6 females from group 2): grade III, 2 patients (1 male from group 1, 1 male from group 2) and grade IV, 1 female from group 1.

The pattern of thymic pathology encountered in group 1 patient was hyperplasia (4 cases), atrophy (one case) and thymoma (one case). The information about the thymic histology in the other 3 patients who underwent thymectomy in other facilities was not available. The thymus was enlarged in one patient in group II on neuroimaging.

No case of drug-induced MG was seen. The main precipitating factors for MG were pregnancy (4 cases) and a preceding febrile illness (1 case). Although none of the patients had clinical or biochemical evidence of thyroid dysfunction, connective tissue disease or malignancy, only one patient had positive smooth muscle antibodies and anti-DNA titres. Nine patients had positive ACh receptor antibody.

In addition to anticholinesterases (Pyridostigmine mainly), 12 of the 18 group 2 patients were also on steroids (Prednisone) and 7 had concomitant azathioprine. After thymectomy the patients still required regular anticholinesterase therapy, combined with prednisone alone (7 cases) and with both prednisone and azathioprine in 2 cases. The response to treatment was considered good in 25 (93 %) patients: all group 1 patients and 16 of the 18 in group 2 (89 %). No patient was totally free of medication even after thymectomy. Two patients with poor clinical response (both in group 2) were subsequently lost to follow-up before other forms of treatment modalities including immunosuppression could be offered. None of the patients had spontaneous remission. Post-thymectomy complications included transient worsening of MG features (2 cases) and pleural effusion which resolved without significant sequelae in another 2 cases. A patient who developed anoxic encephalopathy following cardiac arrest during thymectomy in another facility was subsequently discharged home ambulating after 4 months stay in KFHU. The associated clinical disorders found among the patients were epilepsy and diabetes mellitus (1 case each). The frequency of major myasthenic symptoms is given in Table 2.

Table 2. **Frequency of major symptoms in Saudis with myasthenia gravis (N=27)**

Symptom	*Frequency*	*%*
Ocular		81.5
Diplopia	22	81.5
Ptosis	20	74.1
Impaired vision	3	11.1
Skeletal		92.6
Proximal weakness	25	92.6
Respiratory	5	18.5
Shortness of breath	4	14.8
Bulbar		29.6
Dysphagia	8	29.6
Nasal quality of voice	5	18.5
Voice change	4	14.8
Nasal regurgitation	4	14.8

DISCUSSION

MG is seen in Saudis and the observed hospital frequency rate suggests that it is not uncommon. The annual incidence rate in this series is similar to those reported from other communities even though meaningful comparison is difficult as different population groups were sampled[10,14-16]. Similarly, the age of onset, peak frequency in the third decade, female preponderance in the younger patients, pattern of weakness including the proportion limited to ocular muscles and clinical grade of severity conforms to the well recognised pattern of MG and experience from other studies and need no further comments[9,17-19].

The absence of a definite bimodal presentation and the second peak frequency described in the older age group in our patients may be associated with the small number of cases assessed. However, it may reflect the age distribution of the community in which less than 5 % are more than 60 years old[20]. Although it is often difficult to extrapolate findings from hospital-based studies to the community and general population, the annual hospital incidence rate found in this study may be a true estimate for the community as the incidence of MG in calendar time and in different populations have been observed to be constant[14].

The absence of other autoimmune associated disorders in our patients in contrast to the experience from other studies is noteworthy and difficult to explain[1,21,22]. Similarly, it is interesting to note the good clinical response to medications including immunosuppressive agents in the male diabetic in this series as other medical diseases including diabetes mellitus may interfere with immunosuppressive therapy in myasthenics[23].

The spectrum and severity of complications observed in our patients on all forms of medications and following thymectomy suggest that these various treatment modalities were well tolerated and are safe. However, the observed low mortality rate may be related to the low frequency of clinical grade IV in our patients. Conceivably, it may suggest under reporting although this is unlikely because only 3 patients (11 %) were lost to follow up. The clinical characteristics of our thymectomised patients are similar to those thymectomised group without ectopic thymus described by Ashour[13]. The absence of ectopic thymus in any of our thymectomised patients may suggest either differences in the surgical approach or the small number of cases in this study. However, it may be an expression of the heterogeneity of MG in Saudis. Although other factors precluded optimal use of thymectomy in this series, the absence of complete remission without the need for supportive medications in our patients is unusual as complete remission has been reported in 20-60 % in other studies[24].

The role of ACh receptor antibodies in the diagnosis and identification of seronegative MG in this environment needs further evaluation. Its limited use in this study and scarcity of facilities for its assay in the Saudi Arabia precludes any definitive speculation taking into consideration that elevated titres are more sensitive than other diagnostic parameters[23].

CONCLUSION

Myasthenia gravis occurs in Saudis at a hospital frequency of 6.5/100,000 population. The clinical features and response to therapy are comparable to those reported from other populations. The present study is hospital-based which may not reflect the true incidence of myasthenia gravis in the population at large. Therefore, the main findings of this study could further be corroborated by undertaking a community-based survey.

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