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Myasthenia gravis in Singapore

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Abstract

The demographics and clinical characteristics of myasthenia gravis in Singapore were reviewed. A total of 133 patients with myasthenia gravis seen in our institute over a seven-year period from 1994 to 2000 were studied. There were 1.6 times more women than men, and majority were ethnic Chinese (90.4%). Their median age at onset was 44 years (range 1 – 80), with a bimodal pattern seen in women. The median disease duration was 77 months (range 0.5 – 516). We found a high occurrence of ocular myasthenia gravis (55%), especially in ethnic Chinese. Thymoma was present in almost half of those who underwent thymectomy. These figures were higher than those reported in other series, but comparable to those in the Chinese communities. Ethnic differences in the clinical presentation of myasthenia gravis were observed.

INTRODUCTION

Myasthenia gravis is a disorder of neuromuscular transmission. It occurs in patients of all ages and in all geographical areas.[1-3] However there were few reports on myasthenia gravis from Asia.[4-8] Singapore is a multi-ethnic nation in South-East Asia with a total population of four million. It comprises Chinese at 77%, Malays at 14%, Indians at 8% and the other ethnic groups at 1%. To our knowledge, a review on the clinical manifestations of myasthenia gravis in Singapore has not been published. We thus conducted this study to provide some insights into this disease in Singapore.

METHODS

We reviewed a total of 133 patients with myasthenia gravis seen in our institute over a seven-year period from 1994 to 2000. Being a major neuroscience institute in Singapore, we had one of the largest collections of myasthenia gravis patients in our country. The registry was derived from hospitalised records, electrophysiological data, and prescription data with 'pyridostigmine' prescribed. The medical records were reviewed and all patients were seen either by the authors or their colleagues. The diagnostic criteria of myasthenia gravis was based on the clinical features of fluctuating weakness and fatiguability, supported by either: 1) a positive tensilon test; 2) repetitive nerve stimulation studies with more than 10% decremental response; 3) single fibre electromyographic features of neuromuscular junction defect; or 4) presence of acetylcholine receptor antibody. Cases such as congenital myasthenia gravis, neonatal myasthenia gravis, penicillamine-induced myasthenia gravis and Lambert-Eaton syndrome were excluded from our study. The disease at onset was graded according to the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification.[9] Each patient also had the disease graded at maximum disease severity according to the Osserman grading. This allowed comparison with previous studies that used similar classification system. Treatment outcomes were available in 92 patients, and the MGFA post-intervention status[9] was used.

RESULTS

A total of 133 patients with myasthenia gravis were reviewed. The overall median disease duration was 77 months (range 0.5 – 516). There were 90.4% Chinese, 5.6% Malays, and 4.0% Indians. Compared to the ethnic distribution in Singapore, the Malays and Indians were significantly under-represented (χ^2=11.26, p=0.004). The overall male to female ratio was 1:1.6. Both ethnic Chinese and Malays

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demonstrated a female predominance. As for the ethnic Indians, there were four times more Indian men than there were Indian women.

The median age at onset of myasthenia gravis was 44 years (range 1 – 80), with no significant differences in ethnic distribution across the different age groups. The women showed a typical bimodal pattern of age group distribution (peaks 40 – 49 years and 60 – 69 years). No particular pattern was observed in men.

At onset of illness, more than half of the 133 patients presented with ocular myasthenia gravis (Figure 1). In fact, ocular symptoms were the predominant initial complaints in 92.5% of the patients (Table 1). At the end of the review period, 37% continued to have localised disease (Osserman grade I), 16% with Osserman grade IIa, 24% with grade IIb, 8% with grade III and 15% with grade IV disease. Two patients had isolated bulbar symptoms. Their diagnoses were delayed by a median interval of three months. The rest of the patients had myasthenia gravis diagnosed within a median interval of 1.5 months from the time of onset of symptoms (range 0 – 240). Ocular myasthenia gravis was prevalent in ethnic Chinese, but not in the other ethnic groups (fig 2). The number of men and women with ocular myasthenia gravis were similar. Slightly more than one-third developed generalised symptoms within a median interval of 27 months (range 1 – 348). Women were more likely to have generalised disease compared to men (trend χ^2=4.11, p = 0.043).

Table 2 shows the response rates of the various confirmatory tests. Compared to patients with generalised myasthenia gravis, those with ocular myasthenia gravis were less likely to have a significant decremental response on repetitive nerve stimulation studies (χ^2=13.71, p<0.001). The following factors did not predict the generalisation of ocular myasthenia gravis: age, gender, race, neurophysiological studies, CT thorax results, anti-skeletal muscle and anti-acetylcholine receptor antibody titres. CT thorax reports were available in 112 patients (58 ocular myasthenia gravis; 54 generalised myasthenia gravis). Abnormal mediastinal mass was present in 36 patients, and 25 of them had thymectomy. Thymoma was confirmed in 72% of these patients. The sensitivity of CT thorax in detecting a thymoma in our series was 82%. Anti-skeletal muscle antibody was tested in 95 patients, with a positive titre present in 37 patients. The positive predictive value of this test in detecting a thymoma was 73%, while the sensitivity of the test was 58%.

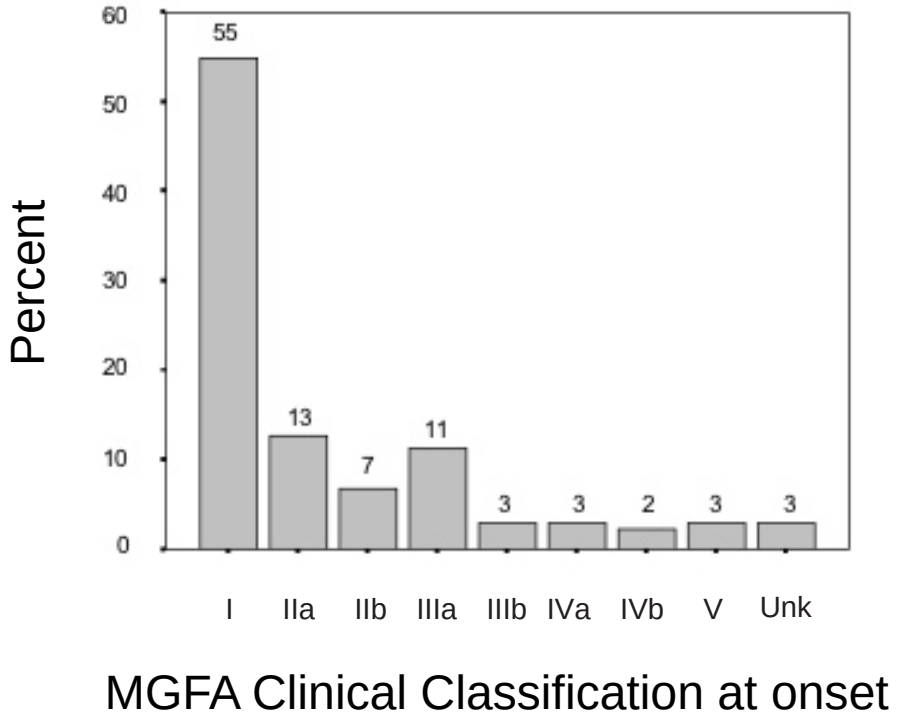
Almost half (43.6%) of the 55 patients with thymectomy had a thymoma (Table 3). All except two patients were Chinese. Those with thymoma were older (median age 42.5 years) than those with thymus hyperplasia (median age 25.5 years). There were fewer women with thymoma (male to female ratio of 1:2.4) than there were women with thymus hyperplasia (male to female ratio of 1:4).

We identified 29 individuals with 34 associated autoimmune conditions. Majority had autoimmune thyroid diseases (19 patients), followed by systemic lupus erythematosus (6 patients), rheumatoid arthritis (3 patients), vitiligo (3 patients), scleroderma (1 patient), idiopathic thrombocytopenic purpura (1 patient), and alopecia areata (1 patient). All were Chinese, and there were 4.8 times more women than men. Ten patients had thymectomy and of these, half were found to have thymus hyperplasia and only one patient had thymoma. The proportion of ocular myasthenia gravis patients among those with autoimmune conditions (37.9%) was almost similar to those without autoimmune conditions (36.5%).

Tumours other than thymoma were present in four patients (breast carcinoma, prostate adenocarcinoma, thyroid papillary carcinoma, and rectosigmoid adenoma). All of them had their tumours removed. Except for the patient with rectosigmoid adenoma whose myasthenia gravis remained ocular, the rest had a more severe clinical course of myasthenia gravis, either developing crisis attacks or generalisation of ocular myasthenia gravis.

Treatment outcomes were available in 92 patients. Almost half showed improvement with treatment and another 40.2% achieved minimal manifestations of myasthenia gravis. Four patients achieved stable remission for at least a year without any treatment, while another four had exacerbation of the disease. Of the four patients with exacerbation of myasthenia gravis, all did not have their thymus removed and two had associated autoimmune conditions. Patients with associated autoimmune conditions generally did worse, with only 27.3% of them achieved minimal manifestations of myasthenia gravis. Of the 55 patients with thymectomy, one patient achieved complete stable remission while another had recurrence of thymoma nine years after thymectomy.

Figure 1. Myasthenia Gravis Foundation of America (MGFA) clinical classification of myasthenia gravis at onset of illness



MGFA Grade 1: ocular MG

MGFA Grade IIa: mild generalized MG, predominant limb or axial muscles involvement

MGFA Grade IIb: mild generalized MG, predominant bulbar or respiratory muscles involvement

MGFA Grade IIIa: moderate generalized MG, predominant limb or axial muscles involvement

MGFA Grade IIIb: moderate generalized MG, predominant bulbar or respiratory muscles involvement

MGFA Grade IVa: severe generalized MG, predominant limb or axial muscles involvement

MGFA Grade IVb: severe generalized MG, predominant bulbar or respiratory muscles involvement

MGFA Grade V: MG cases requiring intubation

Unk: Unknown

Table 1. Frequencies of initial presenting symptoms

Initial presenting symptoms	% of 133 patients
Ocular symptoms	92.5
Upper extremities weakness	32.3
Lower extremities weakness	24.1
Bulbar weakness	22.6
Neck flexor weakness	13.5
Facial weakness	9.8
Respiratory fatigue	6.8

Figure 2. Osserman's grading of myasthenia gravis in different ethnic groups

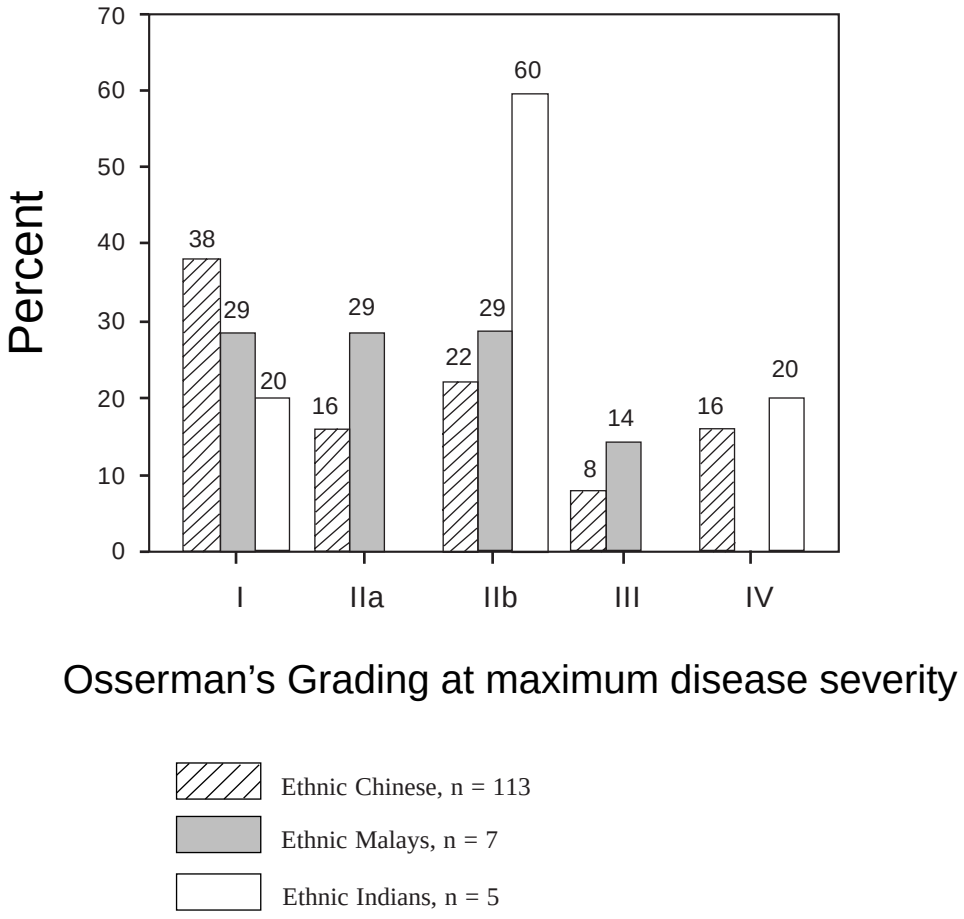


Table 2. Confirmatory investigations

Test	Result	Disease at onset No. (%)			Total
		Ocular	Generalised	Unknown	No. (%)
Tensilon test	**Positive**	**42 (87.5)**	**29 (90.6)**	**1 (100)**	**72 (88.9)**
	Negative	6 (12.5)	3 (9.4)	0 (0)	9 (11.1)
	Total	48 (100)	32 (100)	1 (100)	81 (100)
Repetitive nerve	**Positive**	**33 (55.0)**	**43 (87.8)**	**3 (75.0)**	**79 (69.9)**
stimulation	Negative	27 (45.0)	6 (12.2)	1 (25.0)	34 (30.1)
studies*	Total	60 (100)	49 (100)	4 (100)	113 (100)
Single fibre	**Positive**	**6 (75.0)**	**14 (93.3)**	**1 (100)**	**21 (87.5)**
electromyography	Negative	2 (25.0)	1 (6.7)	0 (0)	3 (12.5)
	Total	8 (100)	15 (100)	1 (100)	24 (100)
Anti-	**Positive**	**6 (66.7)**	**5 (55.6)**	**0 (0)**	**11 (57.9)**
acetylcholine	Negative	3 (33.3)	4 (44.4)	1 (100)	8 (42.1)
receptor antibody	Total	9 (100)	9 (100)	1 (100)	19 (100)
Titre nmol/1	median	1.6	5.1		
	(range)	(0 to 26.2)	(0 to 29.5)		

*comparing ocular myasthenia gravis with generalized myasthenia gravis, $\chi^2 = 13.71$, $p<0.001$

Table 3. Thymus pathologies

	Disease at onset No. (%)		
	Ocular	**Generalised**	**Total**
Thymoma – non invasive	3 (17.7)	12 (31.6)	15 (27.3)
Thymoma – invasive	3 (17.7)	6 (15.8)	9 (16.4)
Hyperplasia	5 (29.4)	5 (13.2)	10 (18.2)
Normal	5 (29.4)	8 (21.1)	13 (23.6)
Atrophy	0 (0)	2 (5.3)	2 (3.6)
Unknown	1 (5.9)	5 (13.2)	6 (10.9)
Total	**17 (100)**	**38 (100)**	**55 (100)**

DISCUSSION

Over the past 20 years, there were reports on the epidemiology of myasthenia gravis in various countries,[3-8,10-13] but few were from South-East Asia. We present, for the first time, the clinical characteristics and demographics of myasthenia gravis in Singapore. Although this is a retrospective review of case series, we have to-date one of the largest series of myasthenia gravis patients in Singapore. All patients with myasthenia gravis seen in our institute over the seven-year period from 1994 to 2000 were included in our study. We observed a predominance of Chinese patients in this series, with under-representation of Malays and Indians. Tan et al[4] also documented a high prevalence of myasthenia gravis among the Chinese patients in Malaysia. Since Singapore is relatively homogenous in terms of access to healthcare services by the various ethnic groups, our study further supports the impression that myasthenia gravis is more common in Chinese than in Malays and Indians.

We also observed a high incidence of ocular myasthenia gravis and thymoma in this study, especially among the ethnic Chinese. More than half of them had ocular myasthenia gravis at onset of illness, and one-third of them remained ocular at the end of the review period. This was higher than the 15 – 26% reported in Caucasians[2,10-12] but comparable to the 46.5% in Taiwan[5] and 47.3% in Hong Kong.[7] The high incidence of thymoma (43.6%) among patients with thymectomy was also comparable to the Hong Kong series at 31 – 48%.[7,14,15] In contrast, only 10 –15% of the Caucasians,[16,17] and 28% of the Japanese[18] had a thymoma. Although selection bias may account for these differences, the similarity with the Hong Kong series is more than coincidental. Both Hong Kong and Singapore's ethnic Chinese ancestors were migrants from Southern China. Genetic variation may contribute in part to the high incidence of ocular myasthenia gravis and thymoma in our patients.

Although previous studies showed men were more likely to have ocular myasthenia gravis[19-21], there was still an overall female predominance among the ethnic Chinese. Unfortunately, the number of Malay and Indian patients in this series were too small to draw any conclusions from them. Nevertheless, a male predominance was observed in ethnic Indians even though they had predominantly generalised disease. Similar observations were reported in India[8] and Sri Lanka.[6]

The proportion of ocular myasthenia gravis patients who developed generalised symptoms, and the time interval to generalisation, did not differ from those of other series.[19,20] The findings on the various confirmatory tests were also comparable to most studies.[13,22,23] Acetylcholine receptor antibody testing was not readily available in Singapore until the last couple of years. Although only 19 patients were tested for acetylcholine receptor antibody, their antibody

titres were similar to those reported in Taiwanese, and were lower than those in Caucasians.[5] The difference may again be attributed to the high proportion of Chinese patients with ocular myasthenia gravis in our series.

The prevalence of associated autoimmune diseases among patients with myasthenia gravis was comparable to those of other studies.[11,24,25] Their presence was associated with a slightly poorer prognosis. A possible link may be an association between the autoimmune diseases and thymus hyperplasia, thus reflecting an overall autoimmune load in these patients.

The role of myasthenia gravis as a paraneoplastic phenomenon is rather intriguing. Besides the high occurrence of thymoma, four patients also had other neoplasms diagnosed. Wilkins et al[26] reported 37 patients with a secondary neoplasm diagnosed either before or at the same time as the thymoma. The significance of the association between myasthenia gravis and neoplasms remain to be determined.

In conclusion, despite the limitations of a retrospective review of case series, additional information on the clinical presentations of myasthenia gravis in Singapore were presented. Ethnic differences may influence the clinical presentation and course of myasthenia gravis in a mixed Asian population.

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