Neurology Asia 2005; 10 : 39 – 45

Effectiveness of immunotherapy in myasthenia gravis: Epidemiological evidence from Sri Lanka

Padma S GUNARATNE *FRCP FCCP*, *Hanna A LARSEN, **Amita K MANATUNGA *PhD*

*Teaching Hospital, Kandy, Sri Lanka; *Department of Psychiatry, Emory University, Atlanta, Georgia, USA; and **Department of Biostatistics, Emory University, Atlanta, Georgia, USA.*

Abstract

Background and objectives: Myasthenia gravis (MG) has been treated with immunosuppressive agents over the last three decades. This study aimed to determine the change in disease pattern that coincides with the advent of immunomodulatory therapy in the Sri Lankan patients. M*ethods:* 112 Subjects diagnosed with myasthenia gravis in the Neurology Unit of the Teaching Hospital in Kandy, Sri Lanka were followed prospectively for 10 years from 1993 to 2003. The clinical features at initial presentation, course of illness, associated autoimmune diseases, MG-related complications, and treatment were documented. *Results:* The ratio of males to females was 2 to 1.2. The distributions of age of onset were not significantly different between males and females. Ptosis and extra ocular muscle palsies were the most common clinical features at presentation; 51% had ocular myasthenia, and 9% had other associated autoimmune disorders. Thymectomy was performed in 13 subjects, and eight subjects developed 23 MG-related crises over 10 years. At the time of analysis, 40% did not require medications for treatment of their MG or needed only anticholinesterase agents to control their symptoms. Symptoms of MG were well controlled with prednisolone (26%) or a combination of prednisolone and azathioprine (28%). Another 5% were resistant to treatment. The mortality rate was 2%.
Conclusion: Myasthenia gravis predominantly affects males in Sri Lanka. No bimodal age distribution is found in the Sri Lankan population. Recent use of immunotherapy has changed the epidemiology of the disease and has increased the percentage of ocular MG and has thereby reduced disability and respiratory failure.

INTRODUCTION

Myasthenia Gravis (MG) occurs in patients of all ages and in all geographical areas.[1-5] It can affect either sex at any age. Data from various reports suggest that it predominantly affects females of childbearing age. [1,5-8] More recent evidence suggests that increasing life expectancy has changed the course of disease and affects more elderly over the age of 50.[8-10] The most common presenting symptoms of MG are ocular, ptosis and diplopia due to extra ocular muscle palsy. Involvment of oropharyngeal muscles causing dysphonia and dysphagia occur in 1/6th and limb weakness occurs in 1/10th of patients.[9] The course of disease is usually progressive. Weakness of muscles is restricted to ocular muscles in 10 – 15% of patients.[11] The subtype, ocular MG, refers to symptoms which remain confined to ocular muscles for more than 2 years. Patients with ocular MG have relatively benign course and do not develop respiratory failure.

The prevalence of MG in the United States is estimated to be 14 in every 100,000.[9] Annual incidence of MG in the county of Osona (Barcelona, Spain) is 21 cases per million inhabitants.[8] The prevalence and incidence of same for Sri Lanka, an island in the Indian Ocean with a population of 18 million, is not entirely known. In 1991, Peiris *et al* reported epidemiological and clinical features in 94 cases of myasthenia gravis seen over 8 years from 1980 at the General Hospital in Colombo, Sri Lanka.[3] According to this report, MG predominantly affected males, and 29% of those individuals had ocular MG.

Anticholinesterase agents were introduced as a form of treatment of myasthenia gravis in 1934.[12] Prednisolone was introduced in the management of MG in the mid-1960s.[13] Since then, other immunosuppressive agents such as azathioprine, cyclosporine A and cyclo-phosphamide have also been used as second line

Address correspondence to: Dr.Padma S Gunaratne MD (SL), FRCP (Glasg), FCCP, Consultant Neurologist, Teaching Hospital, Kandy Sri Lanka. No: 24, Sulaiman Terrace, Colombo 5, Sri Lanka. E mail: pagunara@slt.lk

immunomodulatory agents. According to the data from the pre-immunotherapy era, ocular MG ocured in 15% of myasthenics.[2,11] Numerous reports suggest that the natural history with regard to percentage of ocular MG and sex preference of the disease is changing.[4,8,14-16] This change is likely due to effective treatments which have improved life expectancy in myasthenics today.

The prospective study presented here reports clinical features and course of illness in 112 myasthenics followed prospectively for 10 years, commencing in 1993 at the Teaching Hospital in Kandy, Sri Lanka. Findings of this study was compared the earlier studies two studies of myasthenia gravis in Sri Lanka during two consecutive decades are compared with findings during the pre-immunotherapy era in order to determine the change in disease pattern that coincides with the introduction of immunosuppressive treatment. The objectives were to study the epidemiological and clinical aspects of MG in Sri Lanka, and to assess the outcome of a cohort of patients with MG followed prospectively for 10 years.

METHODS

This study was conducted from July 1993 till September 2003 at the Department of Neurology of the Teaching Hospital in Kandy, Sri Lanka. Inclusion criteria for the study were a positive edrophonium chloride test, improvement after a test dose of oral neostigmine or a decrement of amplitude greater than 10% between 1st and 5th response on repetitive nerve stimulation test. Children less than 12 years, pregnant women and subjects with ischemic heart disease were not subjected to the edrophomium chloride test. Facilities for single fiber EMG and antibody assays for acetyl choline receptors and muscle specific tyrosine kinase were not carried out as they were unavailable as diagnostic tools.

All study subjects were evaluated for their presenting clinical features, course of disease, associated autoimmune disorders, therapeutic modalities used and complications of disease and therapies. They were classified according to Osserman and Genkin classification (I – Purely ocular, II A – Mild generalized, II B – Moderate generalized, III – Acute fulminating generalized signs with prominent bulbar involvement and crises, IV – Late severe generalized and prominent bulbar signs and crises). Fasting blood sugar, renal function tests, liver function tests, serum electrolytes, erythrocyte sedimentation rate, full blood count with picture and chest X-ray were performed in all study subjects. Generalized myasthenics and newly diagnosed ocular myasthenics underwent computerized tomographic (CT) scanning of the chest to find evidence of thymoma. Facilities for thymectomy were not freely available. As such, only subjects with evidence of thymoma, subjects presenting in crisis and some resistant generalised myasthenics underwent thymectomy. Plasma exchange was performed to manage any crisis situations. At the time of enrollment to the study, patients' information was entered in a standard questionnaire. Regular monthly follow-ups were held in the neurology clinic and further information was documented. At the time of analysis they were re-examined for their response to treatment.

All patients in the study were treated with anticholinesterase agents. Except for those with minimal symptoms, all patients received a starting dose of 10 mg of oral prednisolone. The dose was gradually increased to 0.5 – 1 mg per kg body weight over 3 – 4 weeks. Azathioprine, with an initial dose of 50 mg daily, increasing to 2 – 3 mg per kg body weight over the next two months, was prescribed to subjects who did not respond to prednisolone within 3 to 6 months and/or needed long term prednisolone to control symptoms.

Data were summarized by using descriptive statistics for males and females respectively. For continuous outcomes, the two-sample t-test was used to compare the means of males and females. For dichotomized outcomes, Chi-squared test was used to compare proportions. All two-sided p-values were reported.

RESULTS

The previous Sri Lanka study by Peiris *et al*[3] was carried out at the national hospital in the Western Province. The current study was carried out in the largest hospital in the Central province. These are the two most populated provinces in Sri Lanka. Fifty six per cent of the subjects of this study were from the central province and the rest from six other provinces. The ethnic composition of the study subjects were Sinhalese: Tamil: Muslim at a ratio of 11.5: 1: 1. This was comparable to ethnic composition of the population of Sri Lanka.

One hundred and thirteen subjects with characteristic clinical features such as fatigability of skeletal muscles on exertion followed by improvement with rest were screened for inclusion in the study. Of these, 103 patients had positive edrophonium chloride test, 8 had improvement

after a test dose of oral neostigmine and 2 had significant decremental response on repetitive nerve stimulation test. One patient with chronic progressive external opthalmoplegia and false positive edrophonium chloride test was excluded from the study.

Of the 112 subjects included in the study, 63 per cent were males. The age distribution for males at presentation ranged from 1 to 71 years, (mean 40.1 + 15.6 years; median 42 years); and for females, the range was 3 to 64 years (mean 36.3 $\pm$ 17.0 years; median 40 years). The age distribution between males and females were not significantly different (p=0.25), as listed in Figure 1. Most males and females are affected at the ages between 30 to 45 years indicating that there is no bimodal distribution of age of onset of MG.

Demographic information is shown in Table 1. Mean duration of follow up for males was 62 months, (median=71 months) and females 58 months (median= 60 months) and were not significantly different (p=0.60) . Drop out rate was 5 per cent.

Table 2 illustrates the clinical features. Ptosis was the most common, occurring in 93.8 per cent of patients (n=105) at some stage of the illness. Extraocular muscle weakness causing double vision occurred in 77 per cent (n=86) of patients. Other clinical features such as weakness of limbs in 33.6 per cent (n=37.0), bulbar muscle involvement causing dysphagia and dysarthria in 32 per cent and 26 per cent and weakness of neck in 14 per cent and trunk in 14.2 per cent were seen. According to the classification of Osserman and Genkins there were 52 per cent, 21 per cent, 14 per cent, 6 per cent and 5.5 per cent in groups I , II A, II B, III and IV respectively. Fifty-one percent (n=58) of the study group had ocular myasthenia. Of generalized myasthenics 20 per cent developed ocular manifestations earlier than generalized features. Fatigability was elicited in 84 per cent of patients. None of these clinical features were found to be significantly different between males and females (p-values <0.05).

Out of 45 CT mediastinum scans, 5 (11 per cent) showed evidence of thymoma. 11 (10 per cent) had diabetes mellitus at presentation as evident by fasting blood sugar more than 6.8 mmol/l. Nine percent (n=10) of the patients had other associated autoimmune diseases, and the male to female ratio of those was 1 to 4. Most patients with autoimmune disease had generalized myasthenia (70 per cent, n=7). Six patients had thyroid dysfunction. The incidence of both hyper- and hypothyroidism were similar, and two-thirds of the thyroid dysfunction was subclinical. Chronic active hepatitis, polymyositis, rheumatoid arthritis and vitiligo were each observed in separate cases.

Anticholinesterase agents were able to control symptoms in only 5 per cent of subjects with mild disease (n=6), whereas 88 per cent (n=99) needed steroids to control symptoms. Most ocular myasthenics could be managed with steroids combined with anticholinesterase agents. There was a predictable improvement with use of steroids, and most of the patients needed low dose long-term steroids to control symptoms. Besides the usual side effects of the steroids, diabetes developed in 4 subjects, and one elderly individual fractured a femur. Azathioprine was needed in 38 per cent of subjects (n=43) to control symptoms and increased fasting blood sugar made azathioprine the long term immunosuppressive agent of choice in 21 per cent of these cases (n=9). Seventeen percent (n=10) of ocular myasthenics required azathioprine to control symptoms. Adverse events recorded included five patients who developed fever, alopecia, low white blood cell count and two with increased transaminase levels. In the two cases of low white cell count and increased transaminase levels, azathioprine could be reintroduced when the abnormal parameters returned to normal. Thymectomy was performed in 13 (11.6 per cent) subjects. Eight out of 13 had refractory disease for immunosuppressive agents and five of these had CT evidence of thymoma. Histology of thymic tissue showed thymoma in 7, thymic hyperplasia in 3, normal thymic tissue in 2, and a cavernous haemangioma in one. Median age for thymoma was 38 years. Thymoma was predominantly seen in females (5 of 7). The response to thymectomy of these patients was highly variable. Seven subjects had severe forms of the disease with poorly controlled symptoms.

During the study period, eight subjects developed 23 episodes of myasthenic crises. Plasma exchange was adequate to overcome eight episodes. Assisted ventilation was required in 15 situations. The duration of ventilation was 4 to 60 days. Five episodes of myasthenic crisis requiring assisted ventilation occurred while they were on immunosuppressive therapy. All these subjects had histologically proven thymoma. There were two deaths. Both occurred while on assisted ventilation. A 65-year-old man with pulmonary tuberculosis died of respiratory failure. A 45-year-old woman with a history of thymectomy for thymoma and diabetes mellitus died suddenly

Table 1: Demographic data of 112 patients with myasthenia gravis from Teaching Hospital, Kandy, Sri Lanka

	Male (n= 71)	**Female (n=41)**	**p-value**
Mean age in years (S.D.)	40.1 (15.6)	36.4 (17.0)	0.24
Median age in years	42	40	
Mean duration of symptoms in months (S.D.)	82.3 (53.2)	76.9 (57.6)	0.56
Median duration in months	84.0	71.0	
Follow-up in months (S.D.)	62 (39.9)	58 (38.8)	0.60
Median follow-up in months	71	60	

Table 2: Clinical features of 112 patients with myasthenia gravis from Teaching Hospital, Kandy, Sri Lanka

Clinical Features	**n (%)**
Ptosis	105 (94)
External opthalmoplegia	86 (77)
Weakness of limbs	37 (34)
Dysphagia	36 (32)
Dysarthria	29 (26)
Weakness of neck	16 (14)
Weakness of truck	16 (14)
Osserman and Genkins Classification	
I	57 (51)
IIA	20 (18)
IIB	22 (19)
III	7 (6)
IV	6 (5)
Ocular myasthenia	58 (52)
Generalized myasthenia	54 (42)
Thymoma	5 (5)
Associated with other immune disease	9 (10)

Table 3: Comparison between the present study and other studies

	Present Study	**Other Studies**
Male : Female Ratio	2.1 : 1	1: 1.6 (Singapore)[5] 1 : 2 (England)[4] 3 : 1.8 (Sri Lanka by Peiris *et al*[3])
Pattern of age distribution	No Bimodal	Bimodal (Singapore)[5]
Percent of ocular myasthenia	52	29 (Sri Lanka by Peiris *et al*[3]) 46.5 (Taiwan)[9] 37 (Singapore)[5] 47.3 (Hong Kong)[18]
Percent of usage of prednisolone and azathioprine	88% and 35%	40% and 5% (Sri Lanka by Peiris *et al*[3], not known for other studies)

while being ventilated, likely due to myocardial infarction.

At the time of analysis, 40 per cent of patients were off medication or only needed anticholinesterase agents to control symptoms. In another 26 per cent, symptoms could be easily controlled with prednisolone doses equal to or lower than 10mg every other day. In addition to low-dose prednisolone, azathioprine was needed to control symptoms in another 28 per cent. 5.3 per cent had moderately disabling symptoms in spite of using all of the aforementioned modalities. Of the 97 subjects followed for more than 6 months, 96 per cent were in remission for more than 6 months, and of the patients followed up for more than two years (n=74) and 5 years (n=57), 97 per cent and 63 per cent were in remission, respectively.

One hundred and three subjects who were followed prospectively for more than 3 months were assessed for their perceived quality of life. All ocular myasthenics and 89 per cent of generalized myasthenics reported leading a normal life regardless of treatment. Five percent of all the subjects had restricted, but independent lives, given the demands of immunosuppressive therapy and the symptoms of myasthenia gravis. Four of the 17 (23 per cent) individuals who had had the disease for more than 10 years were found to have irreversible weakness. Ptosis, myasthenic snarl, weak eye closure, weak jaw muscles, external opthalmoplegia and weakness of limb muscles were noted to cause permanent disability.

DISCUSSION

MG is a serious, chronic autoimmune neuromuscular disorder. Approximately one third of the study subjects died of MG in the era pre-immunosuppressive therapy and one third were disabled.[17] The chronic course of the illness, spontaneous exacerbations and remissions with fluctuation of symptoms during exacerbations have made the disease difficult to study. At one time, it was found that the prevalence of MG was twice as high in women than men and three times as high during the child bearing period.[1] However, the incidence for both genders was equal before puberty and after the age of forty.[1] The incidence was highest in women in their thirties. In some studies, a late peak was found in older men. According to recent studies, increasing life expectancy in the developed world has affected the trends for gender and the average age of onset for myasthenia gravis.[8-10,16] Accordingly, more elderly after the 50 years of age now develop the disease.[10] Incidence is same for both sexes in this age group.

According to Peiris and colleagues, the male to female ratio of MG is 3 to1.8 in Sri Lanka.[3] The study presented here also showed male predominance over females at a ratio of 2 to1.2. These studies clearly support that myasthenia gravis predominantly affects males in Sri Lanka. The male predominance is seen for myasthenics of all age groups. There was no bimodal age distribution in Sri Lanka. Median age at onset was 40.5 with a peak age distribution for either gender extending from 30 to 60 years. (Table 3)

According to Oosterhuis *et al*, ocular myasthenia (Osserman grade I) occurred in 15 per cent of myasthenics in the pre-immunotherapy era.[2,11] Thirty-seven percent of myasthenics in Singapore are ocular myasthenics.[5] The Peiris *et al* study consisted of 29 per cent ocular cases[3], while the present study showed 52 per cent ocular cases. This figure is comparable to 46.5 per cent in Taiwan[9] and 47.3 per cent in Hong Kong.[18] Higher incidence of ocular cases in the current series could be attributed to more liberal use of immunosuppressive agents. According to the Peiris *et al'* series, use of steroids and azathioprine in Sri Lanka in 1980s were 40 per cent and 5 per cent respectively. In contrast, use of steroids and azathioprine in the present series are 88 per cent and 35 per cent respectively. (Figure 2) Only 3 per cent converted from ocular to generalized myasthenia while on immunosuppressive therapy. Figures with regard to use of immunotherapy for other series were not reported.

Consistent with the findings of Mee *et al*[14], figures of two consecutive studies done in Sri Lanka suggest that early use of immunosuppressive therapy minimizes the incidence of conversion from ocular to generalized manifestations.[14] Immunotherapy has not only minimized the disability but also has reduced the risk of respiratory failure, which is the life threatening complication caused by generalized myasthenia. A high incidence of thymoma (53 per cent) among thymectomized patients was noted in the present study. This figure is comparable to the figures available for Singapore (43.6 per cent)[5] and Hong Kong (31-48 per cent).[18,19] The clinical course of MG was more severe in these patients, relative to non-thymoma patients who received thymectomy. Five of eight subjects who underwent therapeutic thymectomies reported subjective improvement after surgery. Larger case series will be required to establish the

Figure 1: Gender specific age distribution of 112 patients with myasthenia gravis from Kandy, Sri Lanka

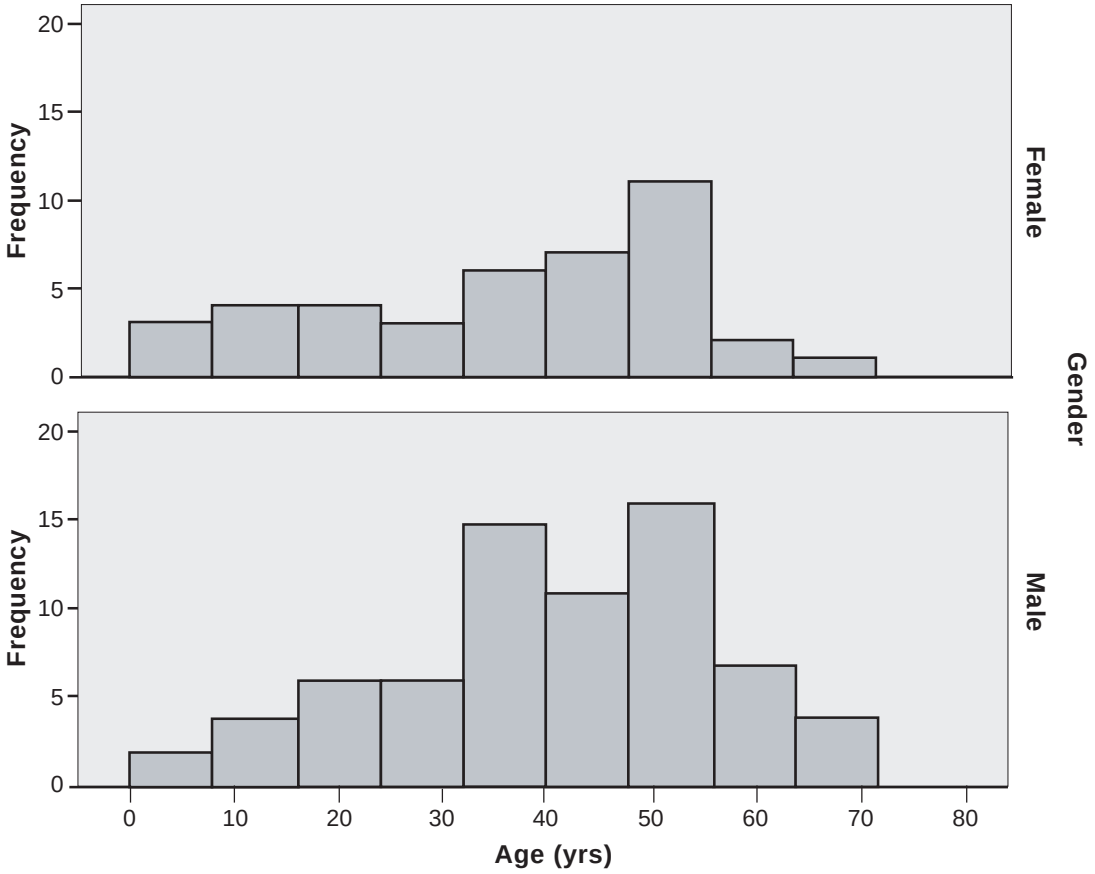
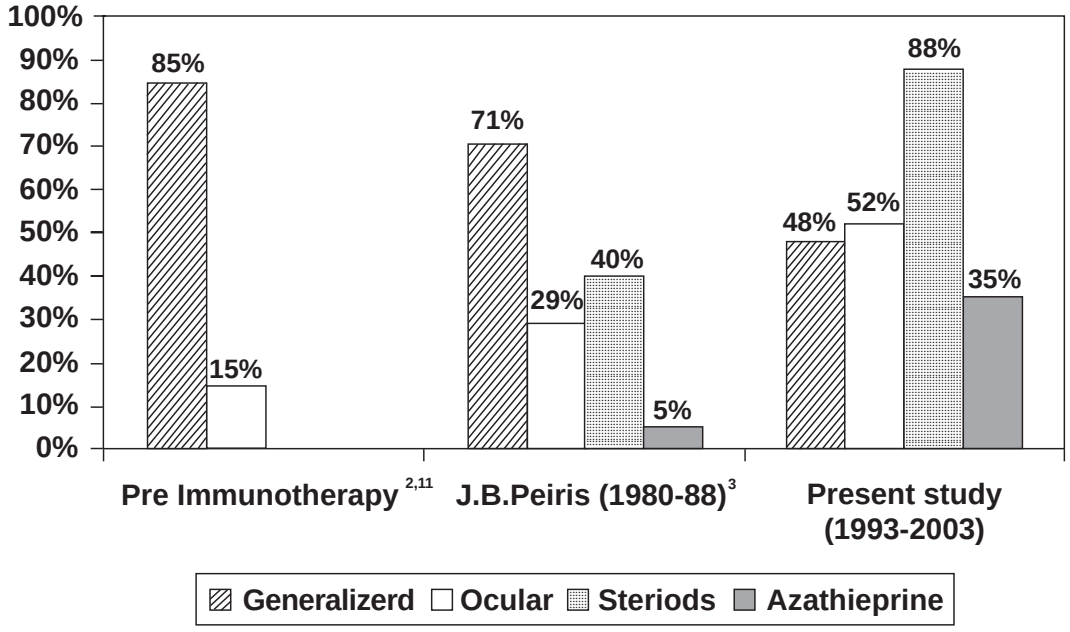


Figure 2: Change in disease pattern with immunotherapy



efficacy of therapeutic thymectomy for severe MG.

Data from older case series of patients indicate 20 to 30 per cent of untreated MG patients died of respiratory failure and spontaneous clinical remission was seen in 20 to 25 per cent of patients.[17] The death rate in the current series was less than 2 per cent and 41 per cent were in total remission. Another 50 per cent were well managed with immunosuppressive agents. These figures lend support to the belief that MG can effectively be treated today. However, the two deaths that occurred during ventilation while the patients were in critical condition highlight the life-threatening nature of MG and the need for optimizing treatment strategy in Sri Lanka.

ACKNOWLDEGEMENT

I wish to thank all medical officers who worked at Department of Neurology since 1993 and anesthetists at Teaching Hospital Kandy, Sri Lanka for the assistance given in taking care of these patients' data collection.

REFERENCES

1. Mantegazza R, Beghi E, Pareyson D, *et al*. A multi centre followup study of 1152 patients with Myasthenia Gravis in Italy. *Journal of Neurology* 1990 Oct; 237(6): 339-44
2. Oosterhuis HJGH. Myasthenia Gravis, a review. *Clinical Neurology and Neurosurgery* 1981; 83(3): 105-35.
3. Peiris JB, Gunathilake SB, Wijeratne C, Gunathilake N. Myasthenia Gravis in Sri Lanka. *Ceylon Medical Journal* 1991; 36: 155-8.
4. Robertson NP, Deans J, Compston DAS. Myasthenia Gravis: a population based epidemiological study in cambridgeshire, England. *J Neurol Neurosurg Psychiatry* 1998; 65: 492-6.
5. Au WL, Das A, Helen TL. Myasthenia Gravis in Singapore. *Neurol J Southeast Asia* 2003; 8: 35-40
6. Drachman DB. Myasthenia Gravis. *N Eng J Med* 1994; 330: 1797-810.
7. Batocchi AP, Majolini L, Evoli A, Lino MM, Minisci C, Tonali P. Course and treatment of myasthenia gravis during pregnancy. *Neurology* 1999; 52 (3): 447-52.
8. Aragones JM, Bolibar I, Bonfill X, *et al.* Myasthenia Gravis - A higher than expected incidence in the elderly. *Neurology* 2003; 60: 1024-6.
9. Chiu HC, Vincent A, Newsom-Davis J, Hsieh KH, Hung TP. Myasthenia gravis: Population differences in disease expression and acetylcholine receptor antibody titers between Chinese and Caucasians. *Neurology* 1987; 37: 1854-57.
10. Aarli JA. Late onset myasthenia gravis. *Arch Neurol* 1999; 56: 25-7.
11. Beekman R, Ehling T, Kuks JBM, Oosterhuis HJGH. Epidemiological data of 100 recent myasthenia patients. *J Autoimmun* 1991; 4(6): xxiii
12. Walker MB. Treatment of myasthenia gravis with physostigmine. *Lancet* 1934; 1: 1200
13. Warmolts JR, Engel WK, Benefit from alternate day prednisone in myasthenia gravis. *N Engl J Med* 1972; 286(1): 17-20
14. Mee J, Paine M, Byrne E, King J, Reardon K, O'Day J. Immunotherapy of ocular myasthenia gravis reduces conversion to generalized myasthenia gravis. *J Neuro-opthalmology* 2003; 23(4): 251-5
15. Sommer N, Sigg B, Melms A, *et al*. Ocular myasthenia gravis: response to long term immuno suppressive treatment. *J Neurol Neurosurg Psychiatry* 1997; 62: 156-62.
16. Phillips LH, Torner JC. Epidemiologic evidence for a changing natural history of Myasthenia Gravis. *Neurology* 1996; 47: 1233-8.
17. Oosterhuis HJGH. The natural course of myasthenia gravis: a long term follow up study. *J Neurol Neurosurg Psychiatry* 1989; 52: 1121-7.
18. Yu YL, Hawkins BR, Ip MSM, Wong V, Woo E. Myasthenia gravis in Hong Kong Chinese. 1. Epidemiology and adult disease. *Acta Neurol Scand* 1992; 86: 113-9.
19. Kay R, Lam S, Wong KS, Wang A, Ho J. Response to Thymectomy in Chinese patients with myasthenia gravis. *J Neurol Sci* 1994; 126: 84-7.