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Factors Associated with Insensitivity to Pyridostigmine Therapy in Thai Patients with Ocular Myasthenia Gravis

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SUMMARY The objective of this study was to determine factors associated with pyridostigmine therapy in patients with ocular myasthenia gravis (OMG). This retrospective study included eighty – five patients with OMG who have been treated with pyridostigmine. Patients were excluded if they were diagnosed as generalized myasthenia gravis within a month after diagnosis or were treated with other medications. Forty-two patients responded to pyridostigmine and 43 patients did not. There were no significant differences in gender, age, the duration of symptoms before treatment, the dosage of pyridostigmine, and the initial presentations of ptosis or diplopia between the two groups. However, an initial presentation of concurrent ptosis and diplopia and the presence of systemic involvement after follow up were significant factors associated with an insensitivity to pyridostigmine in patients with OMG (p = 0.001 and p = 0.01, respectively). Determining these factors could help predict the pyridostigmine response in patients with OMG.

Myasthenia gravis is an autoimmune disorder characterized by an impaired synaptic transmission at the neuromuscular junction. Approximately 75% of all myasthenia gravis patients present with the ocular symptoms of ptosis and/or diplopia with no clinical evidence of bulbar, respiratory and limbal muscle weakness.[1]

Treatment for patients with ocular myasthenia gravis (OMG) includes pyridostigmine, prednisolone and immunosuppressive drugs. In general practice, pyridostigmine is the first line drug but some patients do not respond to pyridostigmine. Some studies found that pyridostigmine alleviates ptosis but may not be effective in resolving diplopia.[2] In Asia, no studies investigated these problems so far. Thus our study was designed to evaluate factors associated with insensitivity to pyridostigmine therapy in patients with OMG.

MATERIALS AND METHODS

The study was conducted at the Out-Patient Department of the Department of Ophthalmology, Siriraj Hospital from 1 January 1994 to 31 December 2004. The study was approved by the Institutional Review Board of Siriraj Hospital. Patients with a diagnosis of OMG who were treated with pyridostigmine were included in the study. All medical records were retrospectively reviewed. The

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diagnosis of OMG was determined primarily by clinical evaluation and a positive response to an anticholinesterase test[3] (neostigmine test or edrophonium test).[4] All OMG patients included in the study had symptoms of weakness and fatigability limited to the extraocular muscles or the levator palpebrae superioris.

Patients were excluded from the study if they were diagnosed as generalized myasthenia gravis (GMG) within one month after diagnosis or were treated with other drugs. Proximal muscle weakness, dysphagia, dysarthria, dysphonia and respiratory difficulties were all considered signs of GMG.

The patients were divided into two groups. The first group comprised of those who responded to pyridostigmine and the second group of those who did not. Response to pyridostigmine was defined as an improvement of ptosis of at least two millimeters and a normalization of the movement of the extraocular muscles and/or of the angle of deviation in the primary gaze.

The patient data recorded included gender, age, the duration from the initial symptoms to the first visit, the dosage of pyridostigmine taken (mg/kg/day), the initial symptoms (only ptosis or diplopia or combined ptosis and diplopia within one month at diagnosis) and the presence of systemic involvement after follow-up.

The Chi-squared and Mann-Whitney tests were used to evaluate the statistical significance of the differences between the two groups. If significant data were found, multivariate analysis (Forward Stepwise Logistic Regression) was utilized.

RESULTS

Eighty-five patients met the inclusion criteria. Forty-two patients responded to pyridostigmine and 43 patients did not. Patients underwent follow-up for a mean of 42.8 months (range 2 months-9 years).

The average age of the patients in the response group was 41 years (SD = 19.3) and in the non-response group 34 years (SD = 23.5). The response group included 17 male patients (40.5%) and the non-response group 17 (39.5%). The average dosages of pyridostigmine were 3.6 mg/kg/day in the response group and 4.0 mg/kg/day in the non-response group. The average duration of symptoms before treatment was 4 months in the response group and 3 months in the non-response group. There was no significant difference in the data described above between the two groups.

Systemic involvement during the follow up period occurred in one patient (2.4%) in the response group and 13 patients (30.2%) in the non-response group, which was significantly different. The initial amount of patients presenting with ptosis was 25 (59.5%) in the response group and 11 (25.6%) in the non-response group, and with diplopia 7 (16.5%) in the response group and 4 (9.3%) in the non-response group. The difference was not statistically significant. But cases presenting with ptosis and diplopia combined were significantly higher in the non-response group than in the response group, i.e. 28 (65.1%) vs. 10 (23.8%), respectively. The severity of ptosis and diplopia was not significantly different between the two groups (data not shown).

Thyroid function tests were done in some of the patients (15 patients [35%] in the response group and 23 patients [53%] in the non-response group). An abnormal thyroid function was found in 2 patients (13%) of the response group and 5 (20%) of the non- response group. In the response group, 1 patient had hypothyroidism and 1 patient hyperthyroidism. In the non-response group, all 5 patients with abnormal results had hyperthyroidism.

The univariate test showed a statistically significant difference between the response and the non-response groups regarding the initial symptoms (p = 0.001), the presence of systemic involvement after follow up (p = 0.002) and the dosage of pyridostigmine treatment (p = 0.016) (Table 1). However, these statistically significant data were further analyzed by multivariate analysis (Table 2). After multivariate analysis, the only factors associated with insensitivity to pyridostigmine therapy were combined initial symptoms of ptosis and diplopia (odd ratio [OR], 6.3 [95% conference interval (CI), 2.1-18.8]) and/or a late onset of systemic involvement (OR, 17.2 [95% CI, 1.9-148.8]). However, after adjustment for the initial symptoms and the late

Table 1 Comparison of clinical factors between response and non-response groups after pyridostigmine therapy in patients with OMG

	Response group N (%)	**Non-response group** N (%)	**Odd ratio** (95%CI)	***p*- value**
1. Number	42	43		
2. Sex*				
- male	17 (40.5%)	17 (39.5%)		1.0
- female	25 (59.5%)	26 (60.5%)		
3. Median age** (years)	41	34		0.361
4. Initial symptoms*				
- Ptosis	25 (59.5%)	11(25.6%)	1.0†	
- Diplopia	7 (16.7%)	4(9.3%)	1.3 (0.2-6.4)	
- Both ptosis and diplopia	10 (23.8%)	28 (65.1%)	6.4 (2.1-20.1)	0.001
5. Median duration from initial symptom to treatment** (months)	4	3		0.334
6. Clinical course of OMG*				
- With systemic involvement	1 (2.4%)	13 (30.2%)	17.77 (2.2-772)	0.002
- Without systemic involvement	41 (97.6%)	30 (69.8%)		
7. Median dosage pyridostigmine** (mg/kg/day)	36	4		0.016

*Statistical test: Chi-square test
**Statistical test: Mann-Whitney test
†Reference: group = ptosis

Table 2 Multivariate analysis of clinical factors determining the response to pyridostigmine treatment in patients with OMG (Forward Stepwise Logistic Regression)

	***p*-value**	**Odd ratio** (95%CI)
OMG with systemic involvement	0.01	17.2 (1.9-148.8)
Initial symptoms		
- Ptosis		1.0
- Diplopia	0.636	1.4 (0.3-6.6)
- Both	0.001	6.3 (2.1-18.8)
Dosage of pyridostigmine	0.059	

systemic involvement, the dosage of pyridostigmine was not associated with an insensitivity to pyridostigmine therapy ($p = 0.059$).

Further multivariate analysis showed that an initial combined symptom of ptosis and diplopia was associated with insensitivity to pyridostigmine therapy compared to an initial symptom of either ptosis or diplopia alone (OR, 5.8 [95% CI, 2.1-15.8]; $p = 0.001$). Another factor associated with insensitivity to pyridostigmine therapy was a late onset of systemic involvement (OR, 16.8 [95% CI, 1.9-145.0]; $p = 0.01$). The dosage of pyridostigmine, however, was again not associated with an insensitivity to pyridostigmine therapy ($p = 0.064$).

DISCUSSION

Myasthenia gravis is characterized by circulating antibodies directed against acetylcholine receptors. In the present study, the factors found to be associated with insensitivity to pyridostigmine were initial symptoms of both ptosis and diplopia and the occurrence of systemic involvement after follow up.

The cause of the insensitivity is probably due to the severity of the disease. Patients who had initial symptoms of ptosis and diplopia combined or had systemic involvement after follow up might have a more severe disease compared to those who did not have such factors. Pyridostigmine is a cholinesterase inhibitor.[1,5,6] The action of this drug is to inhibit cholinesterase, and thus to prevent the destruction of acetylcholine. This is different from the action of immunosuppressive agents that directly attack the abnormal antibodies and prevent them from adhering to the acetylcholine receptors. Immunosuppressive agents attack at the cause of myasthenia gravis. Therefore, patients with more severe disease who do not respond to pyridostigmine may respond to immunosuppressive drugs. Corticosteroid therapy may be warranted for treating patients with OMG at an early stage. Nicholeas *et al.*[3] have shown that the early use of corticosteroids may decrease severity as well as the progression of ocular to generalized myasthenia gravis. The initial steroid has the potential to alter the natural history of OMG from progressing to GMG, but some of the patients require additional immunosuppression. Further study of the actions of corticosteroids and immunosuppressive drugs may help to clarify this issue.

To the best of our knowledge, our report demonstrated for the first time that the duration of symptoms before treatment and the dosage of pyridostigmine received could not predict the pyridostigmine response in Thai patients with OMG. Unlike previous studies[2,7], our data revealed that diplopia alone was not associated with insensitivity to pyridostigmine. The reason for this might be that the characteristics and natural history of OMG are different in Asian and Western patients or because of our small number of patients with diplopia alone. This warrants further study.

Myasthenia gravis patients sometimes have abnormal thyroid function tests. A study from Thailand[8] showed that approximately 23.3% of myasthenia gravis patients had thyroid disease, most of which was thyrotoxicosis. In our study, approximately half of the studied patients were examined for their thyroid function and an abnormal hyperthyroid function was found in about 18.4%.

In retrospective observational studies there is always concern about the limitations of the study design such as selection bias, incomplete data, and small sample sizes. To prevent a possible bias of including only severe cases in our study, being a tertiary care hospital, we included only new patients without previous treatment. Thus, possible selection bias was unlikely. All patients had a complete amount of data. Our sample size seemed adequate, as our results showed significant associations for two factors. On the other hand, diplopia alone was not associated with insensitivity to pyridostigmine in this study, which might be due to the small number of patients with diplopia alone.

We conclude that factors associated with insensitivity to pyridostigmine in patients with ocular myasthenia gravis are systemic involvement after the follow up and initial symptoms of both ptosis and diplopia.

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