Childhood Myasthenia Gravis: Clinical Features and Outcomes

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Objective: *To study the clinical features, treatment, outcome and factors that affected the outcome of myasthenia gravis (MG) in children.*
Material and Method: *Children aged 16 years or less with diagnosed myasthenia gravis (MG) seen at Queen Sirikit National Institute of Child Health over a 15-year period with a minimum follow-up of 6 months were reviewed. Demographic, clinical characteristics, treatment and the outcome were analyzed.*
Results: *One hundred and nineteen MG patients, 100 patients (84%) were ocular MG (OMG) and 19 patients (16%) were generalized MG (GMG). Median age of onset was 4.1 years. OMG patients had the age of onset earlier than GMG patients (p = 0.01). Female to male ratio was 1.8: 1. Ptosis was a clinical feature in 99%, accompanied with ophthalmoplegia in 63%, diplopia in 19.3%, extremity weakness in 13.4%, respiratory muscle weakness in 9%, head tilt in 10.1%, dysphagia in 7.5%, hyperthyroidism in 3.4% and epilepsy in 2.5%. One hundred and six patients who had ptosis as the initial symptom 67% were bilateral ptosis, 33% were unilateral ptosis, 10 patients progressed to GMG in 2 years. Almost all patients were treated with pyridostigmine and prednisolone. At the end of follow-up, 60.5% had pharmacological remission for more than 3 months, 18.5% had complete remission without medication. No definite factors associated with the remission were identified.*
Conclusion: *OMG is the majority of MG patients and the age of onset is earlier than GMG. Early treatment by prednisolone may have the favorable effect on OMG in the progression to GMG and subsequent involvement to the other eye.*

Keywords: *Myasthenia gravis, Pyridostigmine, Prednisolone, Thymectomy, remission*

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Myasthenia gravis (MG) is the most common acquired autoimmune disorder of the neuromuscular junction characterized by weakness and fatigability of skeletal muscle. Fluctuating degree and varying weakness in ocular, limb, respiratory and bulbar muscle is the clinical hallmark of this disease[1,2]. The treatment of MG generally is a combination of symptomatic treatment with anticholinesterase agents, immunomodulating treatment with glucocorticoids, azathioprine, cyclosporine or cyclophosphamide. Some patients have to be treated with thymectomy[1-4]. These depend upon the age of the patients, the severity and progression but there are no points of consensus on the treatment, particularly in children.

The objective of the present study was to analyze the clinical features, treatment, outcome and factors that effect the outcome.

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Material and Method

The authors reviewed the medical records of the patients in QSNICH with diagnosed MG between January 1st, 1995 and December 31st, 2009. The inclusion criteria were fluctuating and variable degrees of muscle weakness, age at onset less than 16 years and minimum follow-up at 6 months. All patients had been diagnosed and treated in the Division of Neurology. Epidemiology, clinical features, type of treatment, outcome and factors were analyzed.

SPSS program was used as analysis tool. The Chi-square test was used to determine the association between the outcome and the factors possibly associated with the outcomes.

Results

One hundred and sixty-three patients with diagnosed MG were reviewed. One Hundred nineteen

cases were fulfilled with the inclusion criteria, 100 (84.3%) patients with pure ocular MG (OMG) and 19 (15.7%) with generalized MG (GMG). The mean age at onset was 4.1 years. The mean duration of follow-up was 5 years, range 1-14.9 years. Female to male ratio was 1.8: 1. Eighty-nine percent of patients had ptosis as the initial symptom, the others were extremity weakness in 3.3%, respiratory muscle weakness in 3.3%, head tilt in 3.3% and dysphagia in 1%. Throughout the follow-up period, all patients except one in generalized MG had ptosis, 32.2% were unilateral, 67.8% were bilateral. Sixy-three percent of the patients had ophthalmoplegia, 19.3% had diplopia, 13.4% had extremity weakness, 10.9% had respiratory muscle weakness, 10.1% head tilt and 7.5% had dysphagia. Eight patients had associated illnesses which were 4 with hyperthyroidism, 1 with hypothyroidism, 3 with epilepsy and 1 with asthma. The Tensilon test was performed in 61 cases, 95% had clinical improvement. Sixty-one percent of patients had pharmacological remission for more than 3 months. 18.5% had complete remission without any medication (Table 1).

In 19 cases of GMG, female to male ratio was 2.1:1, mean age of onset was 7.5 years (range 1.33-14

Table 1. The comparison of clinical features and outcomes between ocular myasthenia gravis and generalized myasthenia gravis

Characteristics	OMG n = 100	GMG n = 19	p-value
Sex			0.71
Male	36	6	
Female	64	13	
Age onset (year),			0.01
< 3	44	2	
3-6	27	4	
> 6-9	11	5	
> 9-12	17	6	
> 12	1	2	
Initial symptoms			
Ptosis	96	10	
Head tilt	4	0	
Limb weakness	0	4	
Respiratory muscle weakness	0	4	
Dysarthria, dysphagia	0	1	
Clinical features			
Ptosis	100	18	0.16
One side	36	2	0.04
Two side	64	16	
Ophthalmoplegia	67	8	0.07
Diplopia	18	5	0.53
Head tilt	11	1	0.69
Extremity weakness	0	16	
Dysphagia	0	9	
Respiratory symptom	0	13	
Provoked with exercise	19	6	0.36
Provoked with Illness	7	3	0.23
Associated illness			0.56
Hyperthyroidism	4	0	
Hypothyroidism	1	0	
Epilepsy	2	1	
Asthma	1	0	
Tensilon test (61)	51	10	0.77
Positive	49	9	
Remission for at least 3 months	60	12	0.80
Complete remission without medication	16	6	0.20

year). Sixty-eight percent of patients presented after the age of 6 years. Sixteen patients had respiratory involvement, 13 patients had extremity weakness, 9 patients had dysphagia and 18 patients had ptosis. Ten patients had ptosis as the initial symptom and developed respiratory muscle weakness or extremity weakness in 1 week-2 years later (Table 1).

Comparison of OMG and GMG, concerning in epidemiology, clinical features and investigated results, seventy-one percent of OMG were less than 6 year-old but 68% of GMG were more than 6 year-old. Age of onset was significantly different in OMG less than GMG. No statistically significance between the groups in gender, ocular involvement, Tensilon test result and the remission (Table 1).

Seventy- two patients (60 with OMG, 12 with GMG) had pharmacological remission and no symptoms for more than 3 months. In comparison of remission and non-remission group, there was no statistical significance in gender, age of onset, clinical features,

Table 2. Comparison of clinical features and treatment in remission and non-remission patients

Characteristics	Remission more than 3 months n = 72	Non remission more than 3 months n = 47	p-value
Sex			0.36
Male	24	18	
Female	48	29	
Age onset (year),			0.15
< 3	28	18	
3-6	20	11	
6-9	13	3	
9-12	10	13	
> 12	1	2	
First symptom			0.32
Ptosis	63	44	
Head tilt	4	0	
Limbs weakness	1	2	
Respiratory muscle weakness	3	1	
Dysarthria, dysphagia	1	0	
Clinical features			
Ptosis	72	46	
One side	23	15	0.40
Two side	49	31	0.55
Ophthalmoplegia	41	34	0.07
Diplopia	13	10	0.42
Head tilt	10	2	0.08
Extremity weakness	10	8	0.41
Dysphagia	5	4	0.51
Respiratory symptom	11	5	0.33
Provoked with exercise	9	1	0.04
Provoked with Illness	16	9	0.44
Associated illness			0.52
Hyperthyroidism	2	2	
Hypothyroidism	1	0	
Epilepsy	2	0	
Asthma	1	0	
Tensilon test (61)	40	21	0.51
Positive	38	20	
Pyridostigmine	69	46	0.48
Prednisolone	58	40	0.35
Thymectomy	10	7	0.52

associated illness, Tensilon test result and types of treatment (Table 2).

There were 22 (18.5%) patients of the present study who had complete remission, without any medication, 16 with OMG, 6 with GMG. Six patients with OMG were treated with Pyridostigmine bromide alone, 10 with OMG and 2 with GMG were treated with Pyridostigmine bromide and prednisolone and 4 with GMG were treated with thymectomy, Pyridostigmine bromide and prednisolone (Table 3). The mean duration of treatment was 6.16 years (range 2.57-12.68 years).

Thymectomy performed in 14 GMG patients and 3 non-responded to medication OMG patients, 9 of GMG and 1 of OMG had pharmacological remission for more than 3 months but only 4 patients of GMG had complete remission without any medication in 4.3-8.5 year (mean 5.8 year) after thymectomy. No thymoma was found, 15 patients showed lymphocytic hyperplasia and 2 patients were normal.

Discussion

The clinical features of childhood myasthenia gravis in the present study revealed female predominance, young age of onset (mean 4.1 year), ptosis as the most common initial symptoms of pure ocular and generalized MG. The majority of patients (84%) were OMG. These findings were similar to reports from China, Korea and Japan by Wong V[5], Kim JH[6] and Fukayama[7] these were different from the reports from Europe and India by Linder A[8] and Ashraf VV[9] which had older age of onset (13.7 year) and the majority were GMG. Grob et al[10] had described the natural history of more than 1,400 myasthenia patients which revealed the initial symptom was ocular symptom in 53%, extra-ocular symptoms in 47%. Most patients exhibited progression of disease, finally 86% were GMG. Afifi and Bell[11] reported progression of unilateral ptosis at onset spread to the other eye in nearly 90%. In the present study findings were different from Grob that the initial symptom was ocular involvement in 89%. Only 10 of 106 patients who had an initial ocular problem progressed to GMG in 2 years, unilateral ptosis at onset but subsequently progressed to the other eye in 67%, less than Afifi and Bell's report. The progression of ocular to be generalized and progression of ocular in the present study differed from other reports[8-11].

The difference in reports from East Asia with Europe and America in terms of gender, age of onset, the progression of the disease and the type of MG may reflect differences in the racial strains and suggest that there are differences in the gene associated with MG between East Asian and Caucasian. Another factor was the early treatment with prednislone which may have an immunosuppressive effect on the natural history of OMG in terms of the progression to GMG and of the progression of the eyes[12].

Pyridostigmine was recommended as an initial medication[13]. Prednisolone was considered to be the most effective oral immunosuppressive agent for the treatment of MG. GMG might have benefit from early thymectomy. Thymectomy in young children was controversial because of the subsequent impairment on immune protection and an enhanced risk of cancer. Andrews et al reported that early thymectomy may be more beneficial than late thymectomy in white patients[14]. In the present study, the physicians used Pyridostigmine as an initial medication together with Prednisolone but did not use a uniform steroid dosing schedule. Most patients were treated with a slowly increasing dose for preventing the transient worsening

Table 3. Comparison of the result of each treatment by complete remission between ocular and generalized MG

Treatment	OMG Complete remission without medication		GMG Complete remission without medication		Total
	Yes	No	Yes	No	
1. Pyridostigmine bromide	6	14	0	0	20
2. Prednisolone	0	3	0	0	3
3. Pyridostigmine bromide and Prednisolone	10	64	2	3	79
4. Thymectomy and Pyridostigmine bromide	0	0	0	1	1
5. Thymectomy Pyridostigmine bromide and Prednisolone	0	3	4	9	16
Total	16	84	6	13	119

by high dose prednisolone, some patients who had a thymectomy were considered in generalized MG, particularly in the respiratory muscle in involved patients. By this treatment, 61% of patients had pharmacological remission and 18.5% had complete remission without any medication. Thymectomy was not proven to be associated with complete remission. The present study findings were similar to Wong and other reports that 29-53% childhood MG had complete remission, a few cases died, 18.5% of patients had complete remission drug-free. The present study showed that MG in children had a better prognosis than adult MG. In most cases, symptoms can be controlled and some had complete remission without medication but required long-term treatment on average over 3 years.

In conclusion, the majority of childhood MG in the present study was OMG and they had an age at onset earlier than GMG. Early treatment by prednislone may have a favorable effect on the natural history of ocular MG in terms of the decrease in the progression to generalized MG and subsequently progression to the other eye. No definite factors associated with remission were identified. The outcome is better than for adults.

Potential conflicts of interest

None.

References

1. Drachman DB. Myasthenia gravis. N Engl J Med 1994; 330: 1797-810.
2. Keesey JC. Clinical evaluation and management of myasthenia gravis. Muscle Nerve 2004; 29: 484-505.
3. Saperstein DS, Barohn RJ. Management of myasthenia gravis. Semin Neurol 2004; 24: 41-8.
4. Richman DP, Agius MA. Treatment of autoimmune myasthenia gravis. Neurology 2003; 61: 1652-61.
5. Wong V, Hawkins BR, Yu YL. Myasthenia gravis in Hong Kong Chinese. 2. Paediatric disease. Acta Neurol Scand 1992; 86: 68-72.
6. Kim JH, Hwang JM, Hwang YS, Kim KJ, Chae J. Childhood ocular myasthenia gravis. Ophthalmology 2003; 110: 1458-62.
7. Fukayama Y, Hirayama Y, Osawa M. Epidemiological and clinical features of childhood myasthenia gravis in Japan. In: Satoyoshi E, editor. Myasthenia gravis-pathogenesis and treatment. Tokyo: University of Tokyo Press; 1981:19-27.
8. Lindner A, Schalke B, Toyka KV. Outcome in juvenile-onset myasthenia gravis: a retrospective study with long-term follow-up of 79 patients. J Neurol 1997; 244: 515-20.
9. Ashraf VV, Taly AB, Veerendrakumar M, Rao S. Myasthenia gravis in children: a longitudinal study. Acta Neurol Scand 2006; 114: 119-23.
10. Grob D, Arsura EL, Brunner NG, Namba T. The course of myasthenia gravis and therapies affecting outcome. Ann N Y Acad Sci 1987; 505: 472-99.
11. Afifi AK, Bell WE. Tests for juvenile myasthenia gravis: comparative diagnostic yield and prediction of outcome. J Child Neurol 1993; 8: 403-11.
12. 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 Neuroophthalmol 2003; 23: 251-5.
13. Snead OC, III, Benton JW, Dwyer D, Morley BJ, Kemp GE, Bradley RJ, et al. Juvenile myasthenia gravis. Neurology 1980; 30: 732-9.
14. Andrews PI, Massey JM, Howard JF Jr, Sanders DB. Race, sex, and puberty influence onset, severity, and outcome in juvenile myasthenia gravis. Neurology 1994; 44: 1208-14.

อาการทางคลินิก ผลการรักษาและปัจจัยที่มีผลต่อการรักษาในเด็กที่เป็น myasthenia gravis

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วัตถุประสงค์: *ศึกษาอาการทางคลินิก ผลการรักษาและปัจจัยที่มีผลต่อการรักษา myasthenia gravis ในเด็ก*
วัสดุและวิธีการ: *ผู้ป่วยเด็กอายุน้อยกว่า 16 ปีที่วินิจฉัยเป็น myasthenia gravis โดยมีอาการอ่อนแรงของกล้ามเนื้อแบบเป็นๆ หายๆ และได้ติดตามการรักษาเป็นเวลาอย่างน้อย 6 เดือน เพื่อยืนยันการวินิจฉัยและผลการรักษาตั้งแต่วันที่ 1 มกราคม พ.ศ. 2538 ถึง 31 ธันวาคม พ.ศ. 2552 เป็นเวลา 15 ปี นำข้อมูลอาการทางคลินิก การรักษา ผลการรักษาและปัจจัยที่อาจมีผลต่อการรักษามาวิเคราะห์หาความสำคัญทางสถิติ.*
ผลการศึกษา: *พบผู้ป่วย 119 ราย เป็น ocular MG 100 ราย และ generalized MG 19 ราย อายุเฉลี่ย 4.1 ปี เพศหญิง: ชาย 1.8: 1 พบอาการหนังตาตกร้อยละ 99, ความผิดปกติในการกลอกตาร้อยละ 63 พบโรคร่วม hyperthyroidism 4 ราย epilepsy 3 ราย tensilon test ให้ผลบวกร้อยละ 91 ด้วยวิธีการรักษาโดยยา pyridostigmine bromide และ prednisolone และการทำ thymectomy ในบางรายพบว่า ร้อยละ 60.5 ไม่มีอาการอ่อนแรงเลยได้นานมากกว่า 3 เดือน ร้อยละ 18.5 สามารถหยุดยาที่ใช้รักษา MG ได้หมด เปรียบเทียบอาการทางคลินิก วิธีการรักษาและผลการรักษาระหว่าง ocular MG กับ generalized MG พบว่า ocular MG มีอาการเมื่ออายุน้อยกว่ากลุ่ม generalized MG อย่างมีนัยสำคัญ แต่ไม่พบปัจจัยที่มีผลต่อการรักษาโรคนี้ นอกจากนี้เมื่อเปรียบเทียบกับการศึกษาอื่นพบว่า prednisolone อาจทำให้การดำเนินของโรคจากชนิด ocular เป็นชนิด generalized ลดลง*
สรุป: *ผู้ป่วย MG ในเด็กส่วนใหญ่เป็น ocular type โดย ocular MG มีอาการเมื่ออายุน้อยกว่ากลุ่ม generalized MG การใช้ยา prednisolone โดยเร็วอาจทำให้การดำเนินของโรคจากชนิด ocular เป็นชนิด generalized ลดลง*