Treatment Outcomes and Predictive Factors in Pediatric Ocular Myasthenia Gravis

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Objective: *To determine demographic data, clinical presentations, investigations, treatment regimens, and clinical outcomes in pediatric ocular myasthenia gravis patients, and to find predictive factors for clinical outcomes such as resolution of disease, development of generalized symptoms, or final amblyopia.*
Material and Method: *This retrospective descriptive study of the medical records of 14 patients (male 6, female 8) less than 15 years that had ocular myasthenia gravis at Chiang Mai University Hospital between January 2006 and December 2012 was done. Univariate analysis was used to evaluate the predictive factors for clinical outcomes.*
Results: *Mean age of onset was 6.96±4.65 years (range 0.58-14 years). All patients presented with ptosis (100%) and 67% with strabismus. The mean of total follow-up time is 6.30±3.84 years (range 1.25-14.25 years). None of the patients developed generalize myasthenia gravis. Only one patient had amblyopia at final presentation. Presenting age, gender, strabismus at initial presentation, and positive neostigmine or edrophonium test did not affect resolution of disease nor final amblyopia.*
Conclusion: *The most common clinical presentation in pediatric OMG was ptosis. Most patients could control the disease only by medications. There were no predictive factors affecting resolution of disease nor final amblyopia.*

Keywords: *Ocular myasthenia gravis, Pediatric, Predictive factors*

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Myasthenia Gravis (MG) is a neuromuscular junction disease caused from reduced acetylcholine receptor (AChR) from the autoimmune antibody. It is characterized by muscle fatigue and weakness. Symptoms tend to worsen by exertion and ameliorate by rest[1-5]. Ocular myasthenia gravis (OMG) affect specifically the ocular muscle, which include levator palpebrae, the two oblique muscles, and the four rectus muscles[1-3]. Patients may present with ptosis, ocular muscle weakness, or diplopia. Some may develop generalized muscular weakness later[5-7].

Thymus gland was found to relate to autoimmunity. Wutthiphan found 10 to 15% of MG patients had thymoma[5]. Somehow, there were found less in pediatric cases[8] and OMG[9]. Performing thymectomy in OMG patients with thymoma could improve symptoms in 67%[10].

Another concern in pediatric OMG is amblyopia. If left untreated, it may affect the patient's vision for the rest of their life. Twenty-one to 52.4% amblyopia were found in first diagnosis of pediatric OMG patients and decreased to 3.0 to 9.5% after treatment[1-3].

Due to its rareness, there are few studies about pediatric OMG available, especially in Asia. There is little information about its symptoms, signs, diagnosis, treatment, and outcomes. The present study could be beneficial for ophthalmologists and general practitioners in understanding the clinical course of disease and potential complications.

Material and Method

Medical records of 12 boys and eight girls aged less than 15 years, diagnosed as OMG in Chiang Mai University Hospital between January 2006 and December 2012 were reviewed retrospectively after the Institutional Review Board approved. The criteria for diagnosed pediatric OMG included (1) age of onset of six months to 15 years, (2) at least one symptom of the following, (2.1) unilateral or bilateral ptosis from history taking or clinical exam without any other cause, (2.2) extraocular muscle weakness with no alternative explanation, (3) no pupillary abnormalities except other associated disease that has pupil involvement, (4) at least one of the following test must be positive, (4.1) fatigability was noted in the effected muscle with worsening of ptosis after asking the patients to

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look upward in a certain of time or progressive weakness of effected ocular muscle when prolong used, (4.2) recovery of ptosis or extraocular muscle weakness after getting rest, (4.3) positive neostigmine or edrophomiumtest, (4.4) positive ice pack test, (4.5) repetitive nerve stimulation test shows abnormality, (4.6) positive enhanced ptosis test, and (5) no generalized symptom by the time of disease onset. These inclusion criteria were modified from Myasthenia Gravis Foundation of America Clinical Classification[12]. Patients were excluded if they had any ocular muscle weakness or fatigue suspected from other disease or had a follow-up time of less than one year.

Demographic data were recorded including gender, age of onset, and clinical presentations. For the visual acuity testing, in verbal children, Allen Pictures and Snellen Chart were used. In preverbal children, fixation behavior was used. Two-line or more difference in best-corrected visual acuity and in preverbal children, inability to fix the target in either eye was defined as amblyopia. Ptosis, strabismus, and ocular duction deficit at initial presentation were observed.

Diagnostic tests, systemic condition, and investigations such as chest X-ray and chest computerized tomography results were collected. Initial and additional treatments were recorded. For the treatment outcomes, patients were classified into one out of four groups using the modification of the Myasthenia Gravis Foundation of America Postintervention Status Categories: complete stable remission, ocular minimal manifestation with medication, ocular minimal manifestation without medication, or persistent generalized symptoms[12]. Treatment outcomes and final clinical presentations were also recorded.

Univariate analysis was used to evaluate predictive factors for resolution of the disease and final amblyopia using SPSS version 17. The *p*-value of 0.05 or less was considered as statistically significant correlation.

Results

Fourteen patients met the inclusion criteria. There were eight female (57.14%) and six male (42.86%). The mean age of presentation was 6.96±4.65 years (range 0.58 to 14 years). For the clinical manifestation at first presentation, initial ptosis was found in all 14 patients (100%), strabismus was found in four patients, and amblyopia was found in one patient (6.67%). Demographic data and clinical presentations are summarized in Table 1.

For the diagnostic test, neostigmine test or edrophonium test was positive in eight out of 13 patients. One patient was negative for neostigmine twice but enhance ptosis revealed positive. Mestinon and prednisolone were started gradually as the therapeutic diagnosis and the patient's clinical signs were improved. Four patients did not performed neostigmine test, three were diagnosed by positive enhanced ptosis test and the other was therapeutic diagnosed by treating with mestinon.

Treating OMG patients was based on their clinical severity. Half of the patients were treated with mestinon and prednisolone. Mestinon only was given in two patients, and one patient was treated with prednisolone and immunosuppressive drug (azathioprine) because he could not tolerate side effect of mestinon. Other detail in treatment regimens are shown in Table 2. The mean follow-up time was 6.30±3.84 years, ranging from 1.25 to 14.25 years.

Chest X-ray was done in nine patients and all revealed negative result. Eight patients underwent chest-computed tomography to evaluate for thymus lesion. Four patients were found positive (one found bulging of thymus gland and the rest were suspected thymoma). Three out of four patients who had positive results in chest-computed tomography underwent thymectomy. Thymic hyperplasia was confirmed

Table 1. Demographic data and clinical presentations of pediatric ocular myasthenia gravis

Demographic data and clinical presentations	No. of patients
Gender	
Male	6/14 (42.86%)
Female	8/14 (57.14%)
Age at onset (years), mean ± SD (range)	6.96±4.65 (0.58-14.00)
Follow-up time (years), mean ± SD (range)	6.30±3.84 (1.25-14.25)
Ptosis at initial presentation	14/14 (100%)
Strabismus at initial presentation	4/6 (67%)
Positive neostigmine or edrophonium test	8/13 (62%)
Abnormal repetitive nerve stimulation test	1/2 (50%)
Positive ice pack test	2/2 (100%)
Positive enhance ptosis test	9/10 (90%)
Generalized symptoms	0/14 (0%)
Final ptosis	9/14 (64%)
Final strabismus	5/13 (38%)
Resolution of disease	1/14 (7%)
Final amblyopia	1/14 (7%)

Table 2. Treatment outcomes of pediatric ocular myasthenia gravis

Final treatment regimen	CSR	MM without med	MM with med	Genrealized symptoms	Final amblyopia
No treatment	1	0	0	0	0
Pyridostigmine	0	0	2	0	1
Pyridostigmine + steroid	0	0	7	0	0
Steroid + immunosuppressant	0	0	1	0	0
Pyridostigmine + thymectomy	0	0	1	0	0
Steroid + thymectomy	0	0	1	0	0
Pyridostigmine + steroid + thymectomy	0	0	1	0	0
Total	1 (7%)	0	13 (93%)	0	1 (7%)

CSR = complete stable reremission; MM = minimal manifestation; med = medication

pathologically in two patients, another one showed thymic tissue with fatty involution.

In our series, no patient developed generalized myasthenia gravis during the treatment period. One was in complete stable remission of the disease and the rest were categorized in ocular minimal manifestation with medication as shown in Table 2.

For the final clinical outcomes, unilateral, and bilateral ptosis were presented in 6/14 (43%) and 3/14 (21%) patients respectively. Final strabismus in primary position was presented unilaterally and bilaterally in 4/13 and in 1/13 patients respectively. Ocular duction deficit was presented in 8/14 patients (57.14%) patients.

Only one patient (7.14%) developed amblyopia in our study. She still had remaining ptosis, right esotropia, and right ocular duction deficit in the final visit. Her final visual acuity was 2/60 right eye and 6/6 left eye respectively.

For predictive factors using univariate analysis in the present study, there was no predictive factor affecting the resolution of the disease nor final amblyopia as shown in Table 3.

Table 3. Predictive factor analysis of final treatment outcomes in pediatric ocular myasthenia gravis

Predictive factors	Resolution of disease	Final amblyopia
Presenting age	$p = 0.84$	$p = 0.24$
Gender	$p = 0.41$	$p = 0.41$
Strabismus at initial presentation	$p = 0.36$	$p = 0.36$
Positive neostigmine or edrophonium test	$p = 0.26$	$p = 0.75$

Discussion

Fourteen patients presented with pediatric OMG were reviewed in our study. The mean age when presented at first clinical presentation was quite different from other studies in which some of other literatures showed early presentation of the disease[2,3]. The female to male ratio in our data was 1.3:1, which quite similar to other studies[1,3,6]. The difference of mean age at presentation probably due to different inclusion criteria and the number of sample size of each study.

All patients in our study presented with ptosis (100%), and 67% presented with strabismus, similar to previous study[1]. The result might be different from other studies either from Asians[2,5,6] or western countries[3]. Nevertheless, because of the nature of the disease, the duction deficit was highly variable in each visit. Most patients were asymptomatic but a few of verbal children complained about intermittent diplopia. Because all our patients were children, gaining the information about the initial specific symptoms might be difficult.

The most common mode of investigations in our hospital was a trial of neostigmine test and edrophonium test. Eight out of 13 patients whose results were positive, which yielded 62% sensitivity, were concordant with Afifi and Bell[13]. One patient was diagnosed based on clinical examination, history, and a positive response to pyridostigmine therapy, though he had two negative results for neostigmine test[6]. Five patients did not undertake neostigmine test; one was diagnosed by using repetitive nerve stimulation test, and the rest using clinical examinations and the responses to pyridostigmine therapy. Although our series did not use edrophonium test as most of other studies[1-3], both neostigmine and edrophonium tests

might be compatible due to their diagnostic yield[13]. Regarding to long-acting anticholinesterase effect of neostigmine, we needed more time to monitor for patient's safety.

Seventy-five percent of MG patients usually have abnormalities of thymus gland[5]. Leeamornsiri et al undertook chest computed tomography in eight patients with pediatric OMG and found abnormal thymus gland in three patients (2 lymphoid hyperplasia, 1 thymoma)[6]. In our series, chest computed tomography was done in eight patients and four were found with positive result in thymus abnormalities. Three patients had thymectomy. Pathologically, thymic hyperplasia was found in two out of three patients, and the other revealed thymic tissue with fatty involution. There was no thymoma in our study. The hyperplastic thymus is presumed to be the site of immune against AChR and a source of anti-AChR antibodies, while the pathogenic role of thymoma is still unclear[14]. The three thymectomized patients required medication to stabilize the disease, but they could taper dosage or number of medication during follow-up. The indication for thymectomy in OMG is highly controversial. One condition that surgery might be considered is the suspicion of thymoma[15,16]. Some authors consider thymectomy in OMG to prevent disease progression rather than to relieve clinical symptoms[17]. In the present study, chest computed tomography results revealed thymoma; therefore, performing thymectomy in these patients were reasonable and the three patients did not progress to generalized MG in at least five years of follow-up.

Our patients were treated with combination of pyridostigmine and prednisolone or pyridostigmine alone as a maintenance therapy in eight and three patients respectively. One was treated with azathioprine combined with prednisolone because he could not tolerate the side effect of pyridostigmine. Another one was treated with steroid only. Other studies reveal that pyridostigmine alone may not adequately control the disease in more severe patients; therefore, immunosuppressive drug has to be added[2,3,6,7]. Even though most of our patients categorized in ocular minimal manifestation with medication, there was no generalized MG found in our series.

Finally, another important aspect of concern in pediatric OMG is amblyopia. Kim et al[2] was found amblyopia in five patients in their series. While four patients were treated successfully, one had persistent amblyopia. Our series found one asymptomatic amblyopic child, probably unrecognized during follow-up. Thus, treatment for this condition is necessary and should be prompt to prevent final amblyopia.

Limitations of the present study were a retrospective nature, thus incomplete and varied data documentation.

In summary, pediatric ocular myasthenia gravis is a rare disease. This study could be widening our horizons to understand more about its natural history and ophthalmic involvement including clinical outcomes and final amblyopia from the investigations and treatment of this disease in Northern Thailand. Regular ophthalmologic follow-up is needed in children with OMG to prevent amblyopia.

What is already known on this topic?

The clinical presentations and clinical course of pediatric ocular myasthenia gravis have been described in the past. Thymoma is rare in pediatric cases and ocular myasthenia gravis. Additionally, thymectomy in ocular myasthenia gravis may prevent disease progression.

What this study adds?

An overview of the clinical presentations and clinical course of pediatric ocular myasthenia gravis in Northern Thailand. The investigations and treatment of pediatric ocular myasthenia gravis in Northern Thailand was described in detail.

There was no thymoma found in our study. Additionally, there were no predictive factors affecting the resolution of the disease nor final amblyopia. Finally, regular ophthalmologic follow-up is needed in children with OMG to prevent amblyopia.

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Potential conflicts of interest

None.

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ผลการรักษาและปัจจัยพยากรณ์โรคของผู้ป่วยกล้ามเนื้อตาอ่อนแรงในเด็ก

ปาริฉัตร ไกรทัศน์, ลินดา หรรษภิญโญ, ประภัสสร ผาติกุลศิลา

วัตถุประสงค์: เพื่อศึกษาลักษณะทางคลินิกในผู้ป่วยเด็กกล้ามเนื้อตาอ่อนแรงชนิด myasthenia gravis และวิเคราะห์ปัจจัยพยากรณ์โรคต่อผลการรักษาในโรงพยาบาลมหาราชนครเชียงใหม่

วัสดุและวิธีการ: การศึกษาย้อนหลังเวชระเบียนของผู้ป่วยเด็กอายุระหว่าง 6 เดือน ถึง 15 ปี ที่มีภาวะกล้ามเนื้อตาอ่อนแรงชนิด myasthenia gravis ที่รักษาในโรงพยาบาลมหาราชนครเชียงใหม่ ตั้งแต่ เดือนมกราคม พ.ศ. 2549 ถึง ธันวาคม พ.ศ. 2555

ผลการศึกษา: มีผู้ป่วย 14 ราย แบ่งเป็นเพศชาย 6 ราย เพศหญิง 8 ราย พบว่าผู้ป่วยมีอายุเฉลี่ย 6.96±4.65 ปี (ช่วงอายุตั้งแต่ 0.58 ปี ถึง 14.0 ปี) ผู้ป่วยมีอาการหนังตาตก 100% อาการตาเหล่ 67% ระยะเวลาในการรักษาต่อเนื่องเฉลี่ย 6.3±3.84 ปี (ช่วงระยะเวลาตั้งแต่ 1.25 ปี ถึง 14.25 ปี) ในการศึกษานี้ไม่พบผู้ป่วยกลายเป็นกล้ามเนื้ออ่อนแรงชนิด myasthenia gravis ทั่วร่างกาย โดยการหายของโรค อาการตาเหล่หรือภาวะตาขี้เกียจหลังการรักษาไม่ขึ้นกับอายุที่มาพบแพทย์ เพศ อาการตาเหล่ในครั้งแรกที่มาพบแพทย์ ผลตรวจ neostigmine หรือ edrophonium ที่เป็นบวก

สรุป: อาการหนังตาตกเป็นอาการที่พบมากที่สุดในโรคกล้ามเนื้อตาอ่อนแรงชนิด myasthenia gravis ในเด็ก ผู้ป่วยส่วนใหญ่สามารถควบคุมโรคได้โดยการรับประทานยา ไม่พบปัจจัยพยากรณ์โรคที่ส่งผลถึงการหายของโรคและภาวะตาขี้เกียจ