JUVENILE MYASTHENIA GRAVIS: A LONGITUDINAL STUDY FROM THAILAND

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Abstract. Juvenile myasthenia gravis (MG), a rare condition of childhood, is an acquired autoimmune disorder of neuromuscular transmission caused by antibodies directed against acetylcholine receptors at the neuromuscular junction. Information about the clinical features and treatment of juvenile MG in Asians is scarce. Accordingly, the aim of this study was to investigate the clinical characteristics, treatment, and outcomes of juvenile MG at Thailand's largest tertiary referral center. This retrospective study included patients diagnosed with juvenile MG at Siriraj Hospital during the January 1996 to December 2013 study period. Seventy-one patients (35 boys) with a median age of 4.3 years were included. Of those, 49 had ocular MG and 22 had generalized MG. Median duration of follow-up was 3 years (range: 1-16.7). Clinical presentations included ptosis/diplopia, limb weakness, bulbar symptoms, respiratory impairment, and myasthenic crisis. All patients received cholinesterase inhibitor as first-line treatment. Glucocorticosteroid and/or steroid-sparing agents were used as an adjuvant treatment in 52% of patients. Seventeen patients underwent thymectomy. Twenty percent of patients were in complete stable remission, 55% were in pharmacologic remission, and 25% were in minimal manifestation status at the last follow-up. Nineteen ocular MG patients required immunomodulation therapy. The majority of patients responded to medical treatment.

Keywords: ocular myasthenia gravis, generalized myasthenia gravis, juvenile, thymectomy, outcome, Thailand

INTRODUCTION

Juvenile myasthenia gravis (MG) is an acquired autoimmune disorder of neuromuscular transmission that is caused by antibodies directed against acetylcholine receptors at the neuromuscular junction. It is clinically characterized by fluctuating and varying degrees of weakness in oculomotor, skeletal, respiratory, and bulbar muscles. MG is classified into ocular and generalized MG (Liew and Kang, 2013), and symptoms can develop at any age. The symptoms and pathophysiology of the disease are similar in both children and adults. However, the epidemiology, prognosis, and treatment of juvenile MG can differ from those of adults (Liew and Kang, 2013). Ocular MG, better long-term outcomes, and absence of thymoma and other immune disorders have been reported more often in children than in adults (Ashraf *et al,* 2006).

Unlike adult MG, clinical characteristics, disease progression, and outcomes of MG have not been well studied in children. Moreover, no standard guidelines or consensus on treatment has yet been established in juvenile MG. Informa-

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tion about the clinical features and treatment of juvenile MG in Asian populations remains scarce. Accordingly, the aim of this study was to investigate the clinical characteristics, treatment, and outcomes of juvenile MG at Thailand's largest tertiary referral center.

MATERIALS AND METHODS

Study subjects

This retrospective chart review included patients diagnosed with and treated for juvenile MG at the Pediatric Neurology Clinic of Siriraj Hospital during the January 1996 to December 2013 study period. Siriraj Hospital is Thailand's largest university-based national tertiary referral center. The protocol for this study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

We included children with a diagnosis of autoimmune MG who were followed for at least one year. Patients with transient MG or congenital myasthenic syndrome were excluded. The following information was collected and analyzed: gender, age at presentation, age of onset, clinical presentation, treatment, duration of follow-up, and clinical outcome.

Severity of MG symptoms was classified as ocular MG, generalized MG, or myasthenic crisis. Diagnosis was made from medical history, physical findings, and one or more of the following diagnostic tests: 1) pharmacologic testing with neostigmine or response to cholinesterase inhibitor treatment trial; 2) electrophysiologic testing with repetitive nerve stimulation (RNS); or, 3) serologic demonstration of acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) antibodies. Post-intervention status was evaluated according to the MG Foundation of America (MGFA) post-intervention status (PIS) guidelines, as summarized in Table 1 (Jaretzki *et al*, 2000).

Table 1
Myasthenia Gravis Foundation of America (MGFA) post-intervention status (PIS).

Complete Stable Remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic Remission (PR)	The same criteria as for **CSR** except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal Manifestation (MM)	The patient has no symptoms or functional limitations from MG, but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of **CSR** or **PR** do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression, but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitor (<120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.

Statistical analysis

Data analysis was performed using PASW Statistics version 18.0 (IBM, Armonk, NY). Patient characteristics were summarized by using descriptive statistics. Data are presented as number and percentage or median and range. Chi-square test was used to test for association between outcomes and the factors associated with those outcomes.

RESULTS

Seventy-one patients (35 boys, 36 girls) with a median age of 4.3 years were included. Of those, 49 (69%) had ocular MG and 22 (31%) had generalized MG. Median duration of follow-up was 3 years (range: 1-16.7). Demographic and clinical data are shown in Table 2, and clinical characteristics of patients with juvenile myasthenia gravis at final follow-up are shown in Table 3. Median age of onset was 4 and 3.2 years old in ocular and generalized MG, respectively. Six patients with ocular MG progressed to generalized MG. Myasthenic crisis was observed in four cases. There was no significant difference in duration of symptoms before diagnosis of MG was made. Seventy (98.5%) of 71 patients presented with ptosis and muscle weakness. Three patients had clinical and laboratory features of Graves' disease that developed at the time of MG diagnosis, 4 months after onset, and 7 years after onset of MG disease.

Diagnostic testing

Pharmacologic testing with neostigmine was positive in all of the 54 patients tested. The other 17 patients responded to cholinesterase inhibitor treatment trial. Other laboratory modalities, including electrophysiology and antibody testing, were not available at our center during the study period.

Table 2
Demographic and clinical characteristics of 71 patients with juvenile myasthenia gravis.

Characteristics	*n* (%) or median (range)
Age at presentation (years)	4.3 (0.75-14.7)
Age of onset (years)	3.9 (0.58-14.6)
Gender: male	35 (49.3%)
Pre-pubertal onset	62 (87.3%)
Duration of symptom before diagnosis (months)	2 (0.5-120)
Follow-up duration (years)	3 (1-16.7)

Table 3
Clinical characteristics of 71 patients with juvenile myasthenia gravis at final follow-up.

Characteristics	*n* (%)	Ocular MG (*n*=49) %	Generalized MG (*n*=22) %
Age of onset, (years) median	-	4	3.2
Ptosis/diplopia	70 (98.5%)	49 (100)	21 (95.4%)
Weakness	16 (22.5%)	0 (0%)	16 (72.7%)
Bulbar symptom	5 (7.0%)	0 (0%)	5 (22.7%)
Respiratory impairment	7 (9.8%)	0 (0%)	7 (31.8%)
Crisis	4 (5.6%)	0 (0%)	4 (18.2%)

Treatment and outcome

Treatments and outcomes are shown in Table 4. Patients were classified as either ocular MG or generalized MG. Cholinesterase inhibitor was the first-line medication used in all patients. Fifty-two percent of patients required adjuvant immunomodulation. Immunomodulation treatment was given in 39% of ocular MG and 82% of generalized MG patients. IVIG and/or plasmapheresis was given to 5 patients during acute exacerbation or crisis. Patients were followed for up to 16.7 years, with a median follow-up duration of 3 years. Six patients with ocular MG progressed to generalized MG at 0.6, 0.9, 1.5, 10, 13, and 14 years after onset of ocular MG. Outcomes were described using MGFA guidelines. At their last reported follow-up visit, 21.1% of patients were in complete stable remission, 53.5% were in pharmacologic remission, and 25.4% were classified as minimal manifestation and all of them were MM-3. Four (5.6%) patients had relapse, which was defined as redevelopment of symptoms after complete stable remission. No correlation was observed between outcome and age of onset, type of MG, or treatment medications used.

Eighteen (25.3%) patients underwent computerized tomography (CT) of the chest, with normal thymus size reported in 15 patients and thymus enlargement found in 3 patients. Seventeen (24%) patients with generalized MG had thymectomy, of which 5 patients had normal thymus and 12 patients had thymic hyperplasia. Of those who underwent thymectomy, 88% had

Table 4
Treatment and outcome of patients diagnosed with juvenile myasthenia gravis.

	Total (*N*=71)	Ocular MG (*n*= 49)	Generalized MG (*n*=22)
Treatment			
Cholinesterase inhibitor	71 (100%)	49 (100%)	22 (100%)
Corticosteroid	31 (43.6%)	16 (32.6%)	15 (68.2%)
Steroid sparing agent	23 (32.4%)	9 (18.4%)	14 (63.6%)
Intravenous immunoglobulin	3 (4.2%)	0 (0%)	3 (13.6%)
Plasmapharesis	3 (4.2%)	0 (0%)	3 (13.6%)
Thymectomy	17 (24%)	0 (0%)	17 (100%)
Combination therapy			
Ach	34 (47.9%)	30 (61.2%)	4 (18.2%)
Ach + C	14 (19.7%)	10 (20.4%)	4 (18.2%)
Ach + C + SS	17 (23.9%)	6 (12.2%)	11 (50%)
Ach + SS	6 (8.5%)	3 (6.1%)	3 (13.6%)
Outcome			
Complete stable remission	15 (21.1%)	8 (16.3%)	7 (31.8%)
Pharmacologic remission	38 (53.5%)	28 (57.1%)	10 (45.5%)
Minimal manifestation	18 (25.4%)	13 (26.5%)	5 (22.7%)
Death	0 (0%)	0 (0%)	0 (0%)

Ach, cholinesterase inhibitor; C, corticosteroid; SS, steroid sparing agent.

clinical improvement. At the last follow-up visit, 30% of patients were in complete stable remission, 35% were in pharmacologic remission, and 35% were in minimal manifestation status.

DISCUSSION

Of the 71 patients included in our analysis, 69% presented with ocular MG, which is consistent with findings from previous studies from Japan, China, and Thailand (Kawaguchi *et al,* 2004; Zhang *et al,* 2007; Sri-udomkajorn *et al,* 2011). However, this finding was inconsistent with prevalence findings from Italy, India, and Canada, which found generalized MG in approximately 70% of cases (Evoli *et al,* 1998; Ashraf *et al,* 2006; VanderPluym *et al,* 2013). This disparity in findings may be explained by differences in the timing of diagnosis, given that some ocular MG patients progress to generalized MG. Follow-up in our study ranged from 1 to 16.7 years. Six patients (8%) developed generalized MG within a range of 0.6-14 years after initially presenting with ocular MG.

Our study found no differences between boys and girls for any outcome of interest (especially in pre-pubertal onset patients), similar to other previous studies in juvenile MG, and regardless of geography or ethnicity (Evoli *et al*, 1998; Ashraf *et al*, 2006; Gao *et al*, 2016). The unavailability of electrophysiology and antibody testing at our center during the study period limited the ability to definitively diagnose MG. Of the 54 patients who underwent neostigmine testing, all had a positive result. The remaining 17 patients responded to cholinesterase inhibitor trial treatment and had clinical course of acquired MG, which confirms no presence of congenital myasthenic syndrome. Eight percent of patients presented with ocular MG and progressed to generalized MG in a period that ranged from 6 months to 14 years after presentation of ocular MG. This finding should alert pediatric neurologists to be aware of delayed symptom progression from ocular MG to generalized MG.

Juvenile MG has a relatively benign course (Seybold *et al,* 1971; Andrews *et al,* 1994; Ashraf *et al,* 2006), however, the treatment regimen guideline for children is not well-established. Generally, cholinesterase inhibitor is the initial treatment in myasthenia gravis patients. Glucocorticoid and/or steroid-sparing agent were the second-line therapy for both generalized MG and uncontrolled ocular MG when they failed to respond to anticholinesterase inhibitor therapy (Liew and Kang, 2013). Up to 38.7% of our ocular MG patients required corticosteroid and/or steroid sparing therapy. As such, ocular MG was not always a mild disease in our population. Corticosteroids were added to the treatment regimen in 43.7% of cases and steroid-sparing agents were added in 32.4% of cases, which is similar to add-on rates reported in a study from Canada (VanderPluym *et al,* 2013). Our findings are also similar to those reported from a study that was conducted at Queen Sirikit National Institute of Child Health (Bangkok, Thailand), relative to clinical characteristics, treatments, and outcomes in juvenile MG (Sri-udomkajorn *et al,* 2011).

Twenty-four percent of patients in our study underwent thymectomy, a rate higher than some studies (Ashraf *et al,* 2006; Sri-udomkajorn *et al,* 2011), but lower than the rate reported by Castro *et al* (2013). Pathologic evaluation of thymuses found thymus hyperplasia in all abnormal thymuses, and none had thymoma. This finding confirms previously reported data that thymoma is less common in juvenile MG than in adult MG (Evoli *et al,* 1998).

This study has some mentionable limitations. First, given the retrospective nature of this study, some patient data may have been missing or incomplete. Second, due to the fact that electrophysiology and antibody testing were unavailable at our center during the study period, some cases of MG may have been inaccurately or late diagnosed. Third, our study population of 71 patients was relatively small. It should be noted,

however, that this condition is rare in children and only 71 cases met our inclusion criteria over a 17-year period. Finally, this study was in patients that were diagnosed and treated at one center, which makes this a single-center study. However, our center is Thailand's largest tertiary referral hospital, which means that we receive complicated cases from all over Thailand. It is, therefore, plausible to assume that our findings are reflective of juvenile MG across Thailand.

In conclusion, consistent with other reports from Asia, ocular MG is more common than generalized MG among children in Thailand. Cholinesterase inhibitor is the most commonly used treatment for MG in Thailand. Although generalized MG often requires adjuvant immunomodulators, such as corticosteroids and/or steroid-sparing agents, approximately 40% of ocular MG patients required adjuvant immunomodulators in our study. This highlights the need for pediatric neurologists in Thailand to observe for insufficient response to cholinesterase inhibitors in children with ocular MG, so that early adjuvant immunomodulatory therapy can be initiated.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

REFERENCES

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.

Ashraf VV, Taly AB, Veerendrakumar M, Rao S. Myasthenia gravis in children: a longitudinal study. *Acta Neurol Scand* 2006; 114: 119-23.

Castro D, Derisavifard S, Anderson M, Greene M, Iannaccone S. Juvenile myasthenia gravis: a twenty-year experience. *J Clin Neuromuscul Dis* 2013; 14: 95-102.

Evoli A, Batocchi AP, Bartoccioni E, Lino MM, Minisci C, Tonali P. Juvenile myasthenia gravis with prepubertal onset. *Neuromuscul Disord* 1998; 8: 561-7.

Gao F, Zhao X, Zhang J, *et al*. Clinical features of patients with myasthenia gravis from the Henan Province, China. *Muscle Nerve* 2016; 53: 711-6.

Jaretzki A, 3rd, Barohn RJ, Ernstoff RM, *et al*. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Ann Thorac Surg* 2000; 70: 327-34.

Kawaguchi N, Kuwabara S, Nemoto Y, *et al*. Treatment and outcome of myasthenia gravis: retrospective multi-center analysis of 470 Japanese patients, 1999-2000. *J Neurol Sci* 2004; 224: 43-7.

Liew WK, Kang PB. Update on juvenile myasthenia gravis. *Curr Opin Pediatr* 2013; 25: 694-700.

Seybold ME, Howard FM, Jr., Duane DD, Payne WS, Harrison EG, Jr. Thymectomy in juvenile myasthenia gravis. *Arch Neurol* 1971; 25: 385-92.

Sri-udomkajorn S, Panichai P, Liumsuwan S. Childhood myasthenia gravis: clinical features and outcomes. *J Med Assoc Thai* 2011; 94 (Suppl 3): S152-7.

VanderPluym J, Vajsar J, Jacob FD, Mah JK, Grenier D, Kolski H. Clinical characteristics of pediatric myasthenia: a surveillance study. *Pediatrics* 2013; 132: e939-44.

Zhang X, Yang M, Xu J, *et al*. Clinical and serological study of myasthenia gravis in HuBei Province, China. *J Neurol Neurosurg Psychiatry* 2007; 78: 386-90.