RESEARCH ARTICLE

MYASTHENIA GRAVIS IN IRANIAN CHILDREN

S. Inaloo MD[1] ,
M. Ghofrani MD [2] ,
H. Eftekharian MD [3]

Abstract:

Objective

This study was undertaken to evaluate the clinical spectrum of myasthenia gravis in children and determine factors that help the clinician in his/her diagnosis and management.

Materials & Methods

A retrospective review was performed on all pediatric patients suffering from myasthenia gravis (M.G) admitted in the department of pediatric neurology of the Mofid Hospital of the Shaheed Beheshti University, between 1994 and 2002.

Results

Of the thirty-two children with M.G. enrolled in our study, seven were suffering from the congenital type while the remaining (25 cases) had the juvenile M.G. Initial symptoms of congenital M.G were ptosis (7/7), limitation of eye movement (2/7) and mild generalized weakness (6/7). Although the Tensilon test was positive in 85% of congenital M.G cases, no myasthenia crisis or spontaneous remission was observed in any of them. In children with juvenile M.G, the age of presentation was 1.2 to 12.5 years, mean age 5.7$\pm$4.2 years (15 girls and 10 boys). The most common presenting symptoms in juvenile group were ptosis in 96% and generalized weakness in 76%. Eight of them (32%) had had at least one myasthenia crisis. EMG was diagnostic in 83% and one case the tensilon test was positive in 84%. One patient had hyperthyroidism and had already been diagnosed with hypothyroidism; two of them were epileptics. Eight patients underwent thymectomy microscopically; in specimens examined, five (62%) showed thymic follicular hyperplasia while in remaining three results were normal. One patient (12.5%) recovered completely after thymectomy with no need for medication during the follow up. Four patients (50%) showed relative improvement and in three cases (37%) improvement was negligible.

Conclusion

The results showed a female to male ratio of 1.5/1 which was correlated to adult M.G. The most common presenting symptoms consisted of ophtalmoplegia, with bilateral ptosis being the most significant. Although this study revealed that thymectomy lacks any remarkable prognostic influence, all patients had thymectomy after two years of disease onset. Some reports have indicated positive results if surgery was performed within two years of onset of disease.

Key words: Myasthenia gravis, Children, Thymectomy, Congenital

1. Assistant Professor of Pediatric, Department of Pediatric ,,Nemazi hospital ,Shiraz University of Medical Sciences
2. Professor of Pediatric Neurology, Department of Pediatric Neurology, Shaheed beheshti University of Medical Sciences
3. Assistant Professor of Anesthesiology, Shiraz University of Medical Sciences
Corresponding author:
Tel: + 98 711 6265024
Fax: +98 711 6265024
Emale: sinaloo@sums.ac.ir

Introduction

Willis first described myasthenia gravis (MG) in 1672 (1) and its onset in childhood was recognized by Erb in 1879(2). Three broad forms of myasthenia in infants and children are are now which consist of known ; autoimmune MG, also known as juvenile myasthenia gravis (JMG), congenital myasthenia gravis (CMG), also known as genetic MG; and transient neonatal MG (3,4). Juvenile myasthenia gravis is an autoimmune disease, in which at least two autoimmune antibody mediated processes underlie autoimmune MG, targeting the acetylcholine receptor (AChR) in the majority and muscle-specific kinase (MuSK) in the minority of patients (5). Congenital myasthenia gravis, a combination of multiple inherited disorders of neuromuscular transmission and neonatal MG, is a transient disease due to placental transfer of antibodies from a myasthenic mother to her baby during pregnancy (6,7). Three to seven percent of MG cases begin before the age of 10 years and 16-30%, before the age of 20 years (8).

Considering the marked differences between the clinical course and management of CMG and JMG, the differential diagnosis between the two is very important. Study and diagnosis of the defect causing CMG requires sophisticated techniques which are not available in most centers(6). We studied a series of childhood MG cases to determine the distinguishing clinical features of CMG and JMG, and to assess their responses to anticholinesterase drugs, steroids and thymectomy.

Patients & Methods

We reviewed the chart of 32 patients with the diagnosis of myasthenia gravis that had been referred to our center between 1994 and 2002. Data was obtained using records of Mofid hospital and telephone interviews. Diagnosis of MG was based on the association of clinical signs of fluctuating weakness of voluntary muscles with fatigability and at least one of the following criteria; unequivocal improvement after I.V edrophonium (positive tensilon test) injection, electrophysiological signs of abnormal neuromuscular transmission such as a decrement more than 10% in compound muscle action potential on low-rate supramaximal repetitive nerve stimulation and ruling out of other causes of muscle weakness. Serum anticholinesterase antibodies were checked only for 5 patients because this test was not available till recently. Severity of disease was graded according to the Osserman and Genkins scale (9). Patients were classified as CMG if they had one of the following: criteria (i) onset before 1 year of age , (ii) onset before 5 years of age and MG history in a sibling or relative and no response to corticosteroid. Other patients were categorized as J.MG.

Parental consanguinity was not included among the criteria since consanguineous marriage is very common in Iran.

Table 1. Severity of disease based on the Osserman and Genkins scale

Group 1	Occular disease only
Group IIA	Mild generalized weakness with no respiratory involvement and good response to anticholinesterase
Group II B	Moderate generalized weakness with no respiratory involvement and less response to drugs
Group III	Acute fulminating onset with respiratory involvement and complete progression within 6 months
Group IV	Late severe myasthenia, developing at least 2 years after the onset of symptoms of group I or II

Results

Thirty-two patients experienced myasthenic weakness which seven of them (2 girls and 5 boys) were affected by CMS; the onset of disease was at birth in 3 patients, and in the remaining 4 it was within the first year. Family history was positive in 3 patients (42.8%), tensilon test was positive in 6 of them (85.7%), EMG with repetitive stimulation was positive in 4 patients (57%). Three patients had only ophthalmic involvement and 3 of them had ptosis associated with mild generalized weakness and one patient had generalized weakness, ptosis and bulbar involvement. None of the patients with CMS developed any acute crisis. One patient was lost in follow up, whereas others were followed for between 3 months to 9 years with a mean follow up of 3.017±3.26 years. Of 6 patients followed, 5 patients showed relatively good response to mestinone; for one patient with ophthalmic myasthenia who had no response to mestinone, steroids and IVIG were tried, but there was no response.

In 25 patients with JMG (15 girls, 10 boys (F/M=1.5/1), the onset age was 1.2- 12.5 years; No patients had a family history of muscle weakness. Six patients (24%) complained of ocular myasthenia (Osserman's-grade I) the other 19 cases had generalized MG; Seven cases (28%) presented with mild disease (grade 2A), 4 (16%) with moderately severe (grade 2B) and very severe MG with respiratory crises (grades 3 and 4) was seen in eight patients (32%). Three patients had 4 crises, while one patient had two. One patient (4%) had hyperthyroidism, one (4%) hypothyroidism and two patients (8%) had epilepsy. Two patients had positive family histories of hypothyroidism in first degree relatives.

Anticholinesterase antibodies were checked in 5 patients, of which in 3 (60%) they were positive. Tensilon test was positive in 21 out of 25 patients (84%). Electrromyogram with repetitive stimulation test was done in 18 patients being positive in 15 (83%). In nineteen patient chests x-ray or CT scans were done; four patients (21%) showed an increased thymus shadow.

Anticholinesterase therapy was administered to all patients, and of these, for ten steroids was also added. For seven patients with myasthenic crises, IVIG was administered, and plasma exchange also used for one patient with a crisis. Follow up duration ranged from between 0.2 to 7 years (mean 3.03±3.2 years).

Thymectomy was performed in seven patients, who did not have a good response to anticholinesterase and steroids. None of them underwent early thymectomy. Histologic examinations showed four of them (57%) had hyperplastic thymuses and three did not. One patient (14%) had complete recovery after thymectomy, needing no medication; two patients (28%) showed relative improvement after thymectomy, while four (57%) showed none.

Five patients (20%) had remission several months, four with generalize MG and one with ocular myasthenia. Three patients treated only with anticholinesterase and one patient with steroid and anticholinesterase and one patient had remission several months after thymectomy. Moderate improvement was observed in 15 patients (60%); five patients (20%) did not have good response, and three patients improved after thymectomy (Table 2).

Discussion

The prevalence of autoimmune MG with onset in the first decade is lower than in the general population, with the exception of Chinese and Japanese patients in whom a high incidence of ocular MG is reported (7). There is no documented information about the prevalence of myasthenia gravis in childhood and adult at our center; during the past 10 years only 25 patients with juvenile myasthenia, 7 patients with congenital myasthenia were recorded at our referral hospital. (This hospital is the most important referral center for pediatric neurology disease in Iran).

Although often difficult, it is important to distinguish the congenital and juvenile forms of childhood myasthenia, because of the differences in their clinical courses and treatment. Symptoms appearing in infancy indicate CMG (6). MG if present in first-degree relatives, strongly suggests hereditary MG syndromes, but the incidence of autoimmune MG in relatives of JMG patients is also higher than in the normal population (4%) (8). Acetylcholin receptor antibody may be absent in up to 44% of JMG cases, limiting the value of this test in the diagnosis of JMG (1). Detailed electrophysiological and morphological studies of the muscle indicate various defects causing CMG; however there are few centers that can perform such evaluations. In our center, diagnosis of congenital MG is based on onset of disease and positive family history.

Table 2. Clinical and paraclinical finding in CMG (N=7) and JMG (N= 25)patients

Findings	CMG	JMG
Age of onset (range)	0-1y/o	1.2- 12.5 y/o
Mean	1.5 y/o	5.5 y/o
Female/ male	2/5	15/10
Family history of MG	3/7	0/25
Associated diseases		
hypothyroidism	0	1
Hyperthyrodism	0	1
epilepsy	0	2
Severity of disease		
Grade 1	3	6
Grade (2A)	4	7
Grade (2B)	0	4
Grade (3,4)	0	8
Tensilon test (positive)	6/7	21/25
Electromyography (positive)	4/7	15/18
Follow up (mean)	3.017 ± 3.2 years	3.03 ± 3.2 years
Response to therapy		
Complete recovery	0	0
good	6	15
No response	1	5

We studied these MG patients for the clinical features, family history, associated autoimmune disease, and response to immunosuppressive treatment. In our study, congenital MG was significantly more common in males (5/2=M/F), results that differed from those of the Anal and et al study; however the JMG ratio however was similar to theirs, i.e. slightly more common in female (9, 10). This result is in contrast with the strong female prevalence in late onset patients (4.2/1) and can confirm the minimal influence of sex hormones on the disease pathogenesis at this age (11). In our study, 28% of JMG patients had only ocular myasthenia, 32% had severe disease with respiratory involvement showing JMS is more benign than late-onset MG, results similar to the Andrews study, and different to the studies of Evoli and Anlar, that show 42.1% with respiratory involvement (9,11,2). Positive family histories of myasthenia reported in our study were 42.8%, as compared to 70% in the Evoli and et al study (11).

The tensilon test and electrodiagnostic study is also beneficial in diagnosis of prepubertal JMG. In our study 84% of JMG, 59% of CMG had positive tensilon test, 83% of JMG, 85.7% of CMG cases had positive EMG findings, compatible with results of other studies (12). In literature on JMG, although the seropositive rate varies (13,1); acetylcholin receptor antibodies was checked only in five patients in our study, being positive in 3, similar to other studies and less than that in the adult onset MG (9,1,2).

Various diseases of autoimmune and non-autoimmune origin have been described in association of JMG in childhood (1, 14, 15). The most common autoimmune

disease associated with JMG in our study was thyroid disease; also epilepsy was more common in JMG in comparison with the general population, but none of CMG cases had any other associated disease. In our study as in other studies, thymoma was not seen in patient pathology reports (9,10,11). Some authors report good results after surgery in prepubertal children (16,17,18), while others describe a lower remission rate in younger rather than in older patients (2,19). In our study also no beneficial result was seen after thymectomy; in 57% there was no response to thymectomy, which might be due to the delay in decision for thymectomy; optimum results are obtained if thymectomy is done within 2 years of onset.

Conclusion

Myasthenia gravis is a relatively rare disease in our center; clinical presentation, response to treatment and prognosis are similar to those described elsewhere, whereas response to thymectomy in our patients is relatively poor because of delays in operation. Hence early thymectomy for myasthenic patient with no response to steroid and anticholinesterase drugs is recommended.

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