Childhood Onset Myasthenia Gravis

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Abstract

The authors share experiences in taking care of 27 cases of childhood onset myasthenia gravis (MGS). In all cases, the diagnosis was confirmed by a combination of clinical examination and Neostigmine test. The majority (92%) had localized ocular myasthenia with median onset of symptoms at 33 months of age. About 24 per cent of them progressed to generalized MGS. A few (8%) presented with respiratory failure that required ventilatory support with onset of symptoms at about 22 months. Thymectomy was performed in 10 cases. Complete and partial remissions were achieved in about 70 per cent and 26 per cent of cases respectively with the combination of an immunosuppressant (azathioprine) and a Cholinesterase inhibitor (pyridostigmine). None experienced a myasthenic crisis with proper management and good follow-up using the above combinations.

Key word : Ocular, Myasthenia Gravis, Childhood, Azathioprine, Thymectomy, Steroid

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Myasthenia gravis (MG) in the pediatric population is a broad term describing several disorders involving the neuromuscular junction.

In adults, myasthenia gravis (MG) has been used exchangably with the term autoimmune myasthenia gravis. However, in the pediatric population, myasthenia gravis encompasses either the disorder with an acquired autoimmune basis as in transient neonatal MG and juvenile MG or the genetically determined disorders of neuromuscular transmission, the Congenital Myasthenic Syndromes (CMSs).

Approximately 10-15 per cent of patients with myasthenia gravis (MG) have the onset in childhood[1,2]. An Oriental population with childhood or juvenile MG, onset of symptoms before 15 years of age, comprised 39 per cent of all myasthenia gravis patients[3].

Myasthenia gravis is not rare but is occasionally seen in pediatric neurology. Patients with myasthenia commonly present with ophthalmological symptoms such as ptosis, strabismus or diplopia, rarely with generalized weakness, bulbar and respiratory symptoms. Managing children with myasthenia gravis is quite challenging. With advances of respiratory care and increasing usage of immunomodulating therapy, morbidity has been decreasing and the mortality rate from myasthenia gravis has been reduced to zero. This report presents the authors' experience in taking care of 27 cases of childhood myasthenia gravis whose symptoms began before 15 years of age.

MATERIAL AND METHOD

The authors reviewed the patient records with the diagnosis of myasthenia gravis that were followed in the Pediatric Neurology Clinic between 1995 and 2001. The records were reviewed for data pertaining to the sex, family history, age at presentation, presenting signs and symptoms, mode and duration of treatment, treatment results and relevant medical history including whether patients underwent thymectomy. Pathology reports were reviewed and documented. Symptoms suggestive of ocular MG were noted. Information concerning neurological examination included an estimation of muscle power in the upper and lower extremities, neck flexor and extensor muscle, bulbar and facial musculature including the palpebral fissure aperture.

The diagnosis of MG was made by using a combination of clinical examination and pharmacologic testing with intramuscular injection of Neostigmine (0.04 mg/kg). A positive response that is increasing muscle strength of the affected muscles or an increase in the aperture of the palpebral fissure is usually noticeable 15-30 minutes after the injection. The disease severity was graded according to the Modified Osserman Classification as either Grade I: Ocular symptom, IIA: mild generalized weakness, IIB: moderate to severe generalized weakness, III: acute severe symptoms, developing over weeks to months or IV as: late, severe with marked bulbar involvement. Chest film, thyroid function test was routinely performed. All patients were asked to attend the Pediatric Ophthalmology Clinic for eye examination.

Patients with pure ocular symptoms or with mild generalized weakness were first treated with pyridostigmine bromide, 7 mg/kg/day or a typical dosage of 30-60 mg orally three times per day. In general, if symptoms were poorly controlled on a maximal dosage of 300 mg/day or if patients experienced side effects of pyridostigmine, immunomodulating therapy would be started. Azathioprine was usually used. It is supplied as a 50-mg tablet and was commenced at a starting dose of 12.5 mg/day, given OD orally, then gradually titrated to a dosage of 2-3 mg/kg/day over a one-month period. White blood cell levels and liver function tests were closely monitored. In some cases with severe ophthalmic involvement, a few weeks of oral prenisolone, 1-2 mg/kg/day, was given on alternate days, which might be used as an adjunt to Azathrioprine while waiting for clinical benefit to show.

Patients with severe generalized weakness or a myasthenic crisis, were given either intravenous immunoglobulin at a dose of 2 g/kg, given over 2-5 days or plasmapheresis, four to six exchanges in which approximately 50 ml/kg of plasma were removed in order to stabilize patients prior to thymectomy. Classical transsternal thymectomy with excision of all mediasthinal thymus was performed in all cases with severe generalized symptoms (Grade III, IV) and in patients with ocular symptoms, either Grade I or II, aged more than 4 years, who failed to respond to the combination of pyridostigmine and azathioprine. In a few cases of severe MG who did not respond to the above protocol, Cyclosporin was used.

The outcome was graded by a method similar to that of Millichap and Dodge[2], either as complete remission, incomplete remission or no response or worsening. Complete remission was defined

as no symptoms or signs of disease either with or without medication. Incomplete remission was defined either as persistent ptosis, diplopia, and intermittent diplopia or limb weakness in spite of appropriate medication.

RESULTS

The present study identified twenty-seven cases of childhood onset MG. The median duration of follow-up of all patients was 48 months (2-7 years). They could be classified into two broad groups, the pure ocular involvement group (Grade I) and the generalized weakness group (Grade III, IV).

Age and Sex Incidence

There were 8 boys and 19 girls. The median age of onset in the pure ocular group was 33 (17-120) months and in the generalized weakness group was 22 (3 -108) months. (Fig. 1) M:F ratios in the ocular group and generalized weakness group were 5:14 and 3:8 respectively.

Family History

No significant family history was noted.

Signs, Symptoms and Disease Severity

The majority of the patients (25 cases; 92%) initially presented with pure ocular symptoms (Grade I) either as unilateral (10 cases), symmetric or asymmetric bilateral ptosis (5 cases) or unilateral or bilateral ptosis with some degree of extraocular muscle weakness (4 cases). The remaining 2 cases (8%) had severe generalized weakness (Grade III, IV) at the onset of symptoms; both of them were referred to us with respiratory failure which required ventilatory support (Table 1) (Fig. 2).

Conversion of Symptoms

Out of 25 cases with pure ocular symptoms, 6 of them (24%) later progressed to generalized weakness within a year or two of the onset of ocular symptoms (Fig. 3).

Associated Diseases

No child had other associated autoimmune disorders e.g. Thyrotoxicosis, SLE. One case had an associated genitourinary tract anomaly with vesicoureteral reflux.

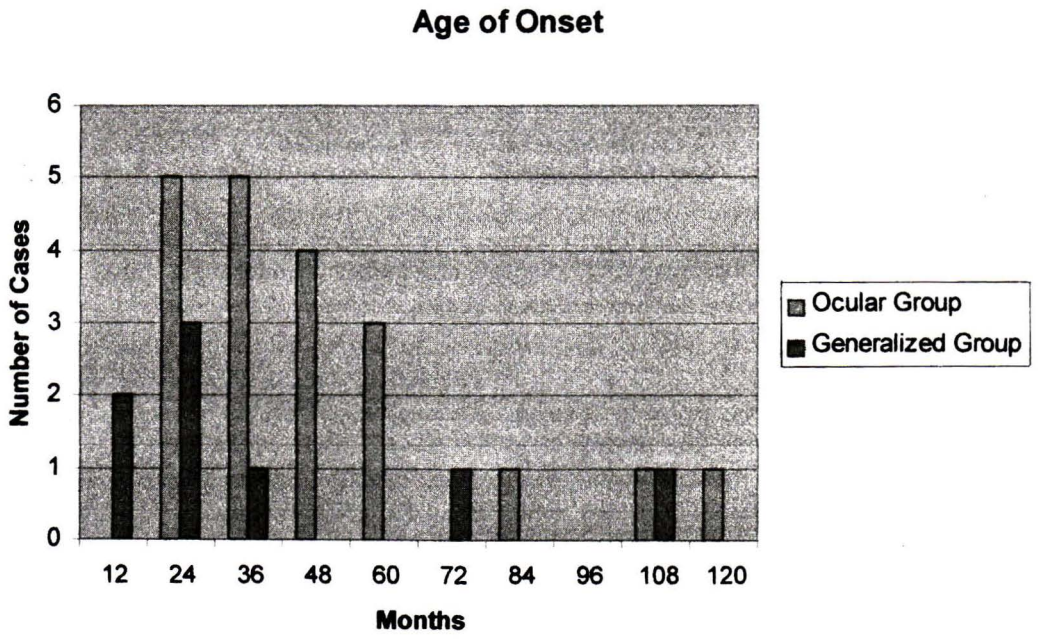

Fig. 1. Age of onset of myasthenia gravis.

Table 1. Clinical and demographic features of children with myasthe gravis according to clinical group (pure ocular *vs* generalized weakness).

	Pure ocular group (cases)	Generalized weakness group (cases)
Number of cases	19	8
M : F	5 : 14	3 : 8
Onset of symptoms (months)	33 (17-120)	22 (3-108)
Presenting symptoms		
• Unilateral ptosis	10	-
• Asym/Sym. bilateral ptosis	5	-
• Bilateral ptosis with ocular muscle weakness	4	-
• Ocular progressing to generalized weakness	-	6
• Generalized weakness at onset, respiratory failure	-	2

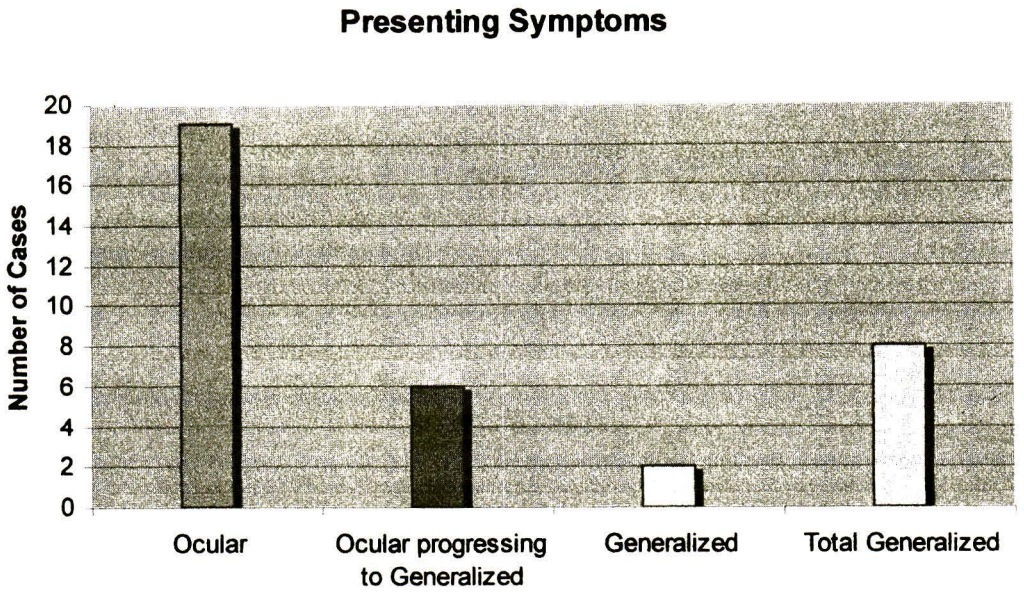

Fig. 2. Presenting signs and symptoms in patiens with myasthenia gravis.

Management

In the ocular group, complete remission was achieved in 13 cases (68%), without medication in 7 cases and with either pyridostigmine or azathioprine alone or a combination in 6 cases. Two patients from the ocular group underwent thymectomy because their symptoms were refractory to all medications.

In the generalized weakness group (Grade III, IV), in order to stabilize the patient prior to thymectomy, intravenous immunoglobulin and plasmapheresis were used in 6 and 4 cases respectively with dramatic improvement. All had thymectomy, followed by oral pyridostigmine and azathioprine. There were no deaths. Complete remission was achieved in 6 cases (75%), off all medications in 3 cases, partial remission and no response in 1 case each. There were two cases, who after thymectomy were refractory to oral azathioprine, so cyclosporin was used instead. In one case, the patient achieved complete remission without any medication, while the other had partial remission. Of the 27 cases that received oral azathioprine, with a dosage range from 12.5-100 mg/day, none experienced severe side effects other than mild, reversible leukopenia.

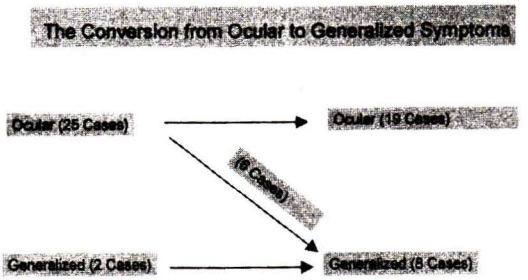

Fig. 3. Conversion from ocular symptoms to generalized symptoms.

Table 2. Outcome and the complication of treatment in children with myasthenia gravis.

	Outcome			
	Pure ocular group (cases)	Generalized weakness group (cases)	Total 27 cases	%
Complete remission	13	6	19	70
• Without medication	7	3	10	37
• With either pyridostigmine, azathioprine, or a combination	6	3	9	33
Incomplete remission with mild ptosis and/or intermittent diplopia, mild generalized weakness	6	1	7	26
No response	-	1	1	4
Severe adverse effect from azathioprine	-	-	-	
Mortality	-	-	-	

Outcome

In the overall experience of 27 cases of childhood onset MGS, complete remission without medication was obtained in 10/27 (37%) and with remisson using either pyridostigmine or azathioprine or a combination in 9/27 (33%). Neither in the ocular nor the generalized group experienced myasthenic crisis or death with the appropriate management and good follow-up (Table 2).

Thymectomy

Classical transsternal thymectomy was performed in 10 cases, 2 of them had ocular MG which was refractory to anti AchE medication and azathioprine. The remainder had generalized weakness. Histopathology revealed thymic hyperplasia in 6 cases and normal tissue in 4 cases (Table 3).

DISCUSSION

In pediatric practice, MG usually presents as either a disorder with an acquired, autoimmune basis as in transient neonatal MG and juvenile MG or genetically determined disorders of neuromuscular transmission, the Congenital Myasthenic Syndromes (CMSs).

Transient neonatal MG occurs after transplacental transfer of maternal acetylcholine receptor (AchR) antibodies. About 12 per cent of children born to myasthenic mothers have this condition[4]. Its natural history has been studied since 1983[5]. They usually have a neonatal onset with systemic and ocular involvement, with recovery by 2 months of age[6]. The management of infantile myasthenia gravis has been reported since 1981[7].

Juvenile AMG arises from the binding and blocking action of AchR antibodies, which together with complement reduce the number of functional AchRs. Juvenile AMG is seen later in life than CMS, although there is overlap between the late-occurring mild CMS and early-onset juvenile AMG, generally between 1 and 2 years of age. Juvenile AMG may be divided into ocular and systemic.

The CMSs are genetic disorders and not associated with autoimmune disease; consequently,

Table 3. Result of transsternal thymectomy according to clinical group (pure ocular *vs* generalized weakness).

	Ocular group (cases)	Generalized weakness group (cases)
Classic transternal thymectomy (10 cases)	2	8
Thymus histology:		
• Thymic hyperplasia (6 cases)	1	5
• Normal thymus (4 cases)	1	3
• Thymoma	-	-

immunosuppressive therapy is not effective. Patients with CMS were often misdiagnosed as non responsive myasthenia gravis. They are caused by structural or functional, presynaptic or postsynaptic abnormalities. These may result in inadequate release of acetylcholine or AchR dysfunction such as slow channel or prolonged open channel syndrome. Most patients are symptomatic in infancy, presenting with feeding difficulty, respiratory dysfunction, ophthalmoparesis, ptosis, hypotonia, and limb fatigability. Those with mild disease may be seen initially in the second year of life or later[8]. The frequency of CMS varies from 8 per cent to 13 per cent in reported series of childhood MG but may be higher where consanguineous marriages are frequent[9].

Of 27 cases in the present series, there were no patients with transient neonatal myasthenia gravis. The youngest patient was a 3-month-old girl with left ptosis who had a clearly positive Neostigmine test. They fall into two broad categories of either autoimmune juvenile myasthenia gravis or a congenital myasthenic syndrome.

In taking care of these patients, the authors faced several constraints from the diagnostic and management point of view.

From the diagnostic viewpoint, the conventional diagnostic tools, such as serum AchR-antibody and repettive stimulation (RS), had low a yield and were not available. Serum AchR-antibody is not routinely available, but it is the most specific and reassuring test supporting the diagnosis. In a pediatric population, it will be positive in only 56 per cent of cases[10], and even less in pure ocular and mild MG types[9-11].

Electrophysiologic testing or RS, is typically recorded in the distal thenar or hypothenar muscle after stimulating the median or ulnar nerve. RS requires special equipment, an Electromyography (EMG) machine along with a qualified, well-trained physician to perform it and, above of all, it is a lengthy procedure. Positive test or a deccremental response in distal muscle was found in only 20-50 per cent of the patients[12]. The chance of finding a positive decremental response will almost doubled to 66 per cent when using proximal muscle stimulation[11] or using a special technique such as sensitization of the ulnar nerve with ischemia[13]. In summary, these require good patient cooperation, which is not possible in children.

All in all, the authors were left with the only option of relying on clinical neurological examination and the pharmacologic response to antiacetylcholine esterase inhibitor. Edrophonium or Neostigmine testing is a sensitive test for MG. Positive results will be seen in up to 90 per cent of juvenile MG cases[11]. A positive test is unable to differentiate between an acquired or genetic etiology. Because CMSs and seronegative autoimmune MG present in early childhood, differentiating these disorders when the family history is negative is often difficult[10]. However, fluctuating weakness or disease severity with a good response to pharmacotherapy or plasmaphreresis favors an autoimmune basis[9,10].

From the management point of view, there is no consensus for childhood MG. The data on the natural history of childhood myasthenia is based on the extrapolated data from adult studies. However, several small case series of childhood myasthenia have been published[2,14,15]. The management of childhood MG, in general, depends on the institution concerned, although some conclusions can be made. Anti-AchE medications e.g. pyridostigmine are used routinely[15]. Thymectomy is recommended for patients with generalized disease, even in a pediatric population[16,17]. A remission rate of 260 per 1,000 person-years was seen during the first year after surgery compared to a sponta-

neous remission rate of 22.4 per 1,000 person-years (16). Plasmapheresis has been helpful in selected cases to maximize patient function prior and after thymectomy and is recommended in severe weakness, respirator dependence, and myasthenic crisis where it is a life saving procedure(18).

In the group of pure ocular MG patients who are refractory to anti AchE medication, management is controversial and there is no consensus. Some prefer thymectomy as the next step(19-21), while others prefer oral corticosteroids(15,22).

In Europe, azathioprine has been used as the first line drug in severely affected patients unresponsive to other forms of therapy. It has been used as a "Steroid Sparing Agent". Most of the reports are from studies in adult patients who have relapsed on prednisolone, or in those who have been taking prednisolone for a long period(23-25). The safety of azathioprine in children has not been established. It has also been used in children refractory to other management modalities in conjunction with plasmapheresis. If azathioprine is used, precautions should be taken to avoid pregnancy because of its teratogenicity.

In the authors' experience, 92 per cent of patients present with ocular symptoms. None achieved complete remission with anti AchE medication alone. When azathioprine was added, 70 per cent of cases achieved complete remission and half of them continued to be in remission after they were off all medication. In the ocular group, only 24 per cent progressed to generalized weakness which is less than in another report, which was around 30 per cent(26). None of the patients experienced severe adverse side effects such as hepatitis or an idiosyncratic reaction to azathioprine.

Thymectomy is a generally accepted mode of therapy in generalized MG as mentioned above. The role of thymectomy in children has recently been reviewed(17). A favorable clinical response and low morbidity and mortality in childhood cases support its use(27-29). It has been shown to be beneficial in adults with exclusive ocular symptoms who had resistance to pyridostigmine therapy or relapse following immunosuppressive therapy (30). One study has proposed early thymectomy in children with myasthenia gravis who are refractory to pyridostigmine and oral steroids(29). However, there is no consensus on this issue in the pediatric population, because its natural history is usually pure ocular symptoms and has a high remission rate compared to adults.

The data on thymus gland pathology are mainly from adult studies. Most patients have a thymic abnormality consisting of thymoma (10-16%), patients more than 40 years old had high levels of AchR antibody. Thymic hyperplasia has been found in 80 per cent(31). In a report of pediatric cases, thymic hyperplasia was found in 50 per cent. None had a thymoma(29). In the present series, no thymoma and thymic hyperplasia were found in 60 per cent of the cases (6/10).

The reminder of the patients (approximately 30% of cases) showed either a partial response (26%) to Anti AchE medication and azathioprine or no response at all (4%). There is a high possibility that this group of patients falls into the category of CMS, until proven otherwise. A definite diagnosis requires *in vitro* electrophysiology studies from a muscle biopsy specimen and intensive molecular genetic studies of the patient's genomic DNA.

SUMMARY

For the treatment of myasthenia gravis in children, the authors are more familiar with the use of long-term oral azathioprine than oral steroid. At a dose of 1-2 mg/kg/day, patients tolerate it well and none experienced severe adverse effects, other than mild leukopenia. Without using oral steroids, complete and partial remissions were achieved in the majority of patients. None experienced a myasthenic crisis. The prognosis of ocular myasthenia gravis is good. A conventional scheme using short-term corticosteroids and long-term oral azathioprine seems adequate to achieve remission in most patients.

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รายงานนี้แสดงถึงประสบการณ์ ในการดูแลผู้ป่วยเด็กที่มีภาวะ myasthenia gravis 27 คน ของหน่วยประสาทวิทยา ภาควิชากุมารเวชศาสตร์ ซึ่งได้ติดตามผู้ป่วย เป็นระยะเวลา โดยเฉลี่ยประมาณ 5 ปี ผู้ป่วยทุกราย ได้รับการวินิจฉัยโดยการตรวจร่างกายและใช้ neostigmine test ผู้ป่วยส่วนใหญ่ (92%) จะมีอาการเฉพาะที่ บริเวณของตา หนังตาตก กล้ามเนื้อตาอ่อนแรง โดยมีอาการและอาการแสดงในระยะเริ่มแรกเมื่ออายุประมาณ 33 เดือน 24% ของผู้ป่วยกลุ่มนี้ จะมีอาการรุนแรงมากขึ้น โดยมีอาการอ่อนแรงของกล้ามเนื้อทั่วทั้งตัวในที่สุด ผู้ป่วยส่วนน้อย (8%) มาพบแพทย์ ด้วยอาการอ่อนแรงของกล้ามเนื้อทั่วทั้งตัว รวมถึงกล้ามเนื้อที่ช่วยในการหายใจ และต้องการเครื่องช่วยหายใจ โดยมีจะอาการและอาการแสดง ในระยะเริ่มแรกเมื่ออายุประมาณ 22 เดือน การผ่าตัดต่อมทัยมัสทิ้งกระทำในผู้ป่วย 10 ราย ผู้ป่วยทั้งหมด 70% อาการหายขาด 26% ของผู้ป่วยอาการดีขึ้นบ้าง และ 4% จะไม่ตอบสนองต่อการรักษา ผู้ป่วยเกือบทั้งหมดอาการจะดีขึ้น โดยไม่ต้องอาศัย steroid แต่ต้องใช้ยากดภูมิต้านทาน zathioprine ร่วมกับ pyridostigmine ภายหลังจากได้รับยาที่ดี และมีการดูแลติดตามผู้ป่วยอย่างใกล้ชิด ไม่มีผู้ป่วยเกิดอาการ myasthenia gravis อีกเลย

คำสำคัญ : กล้ามเนื้ออ่อนแรง, การตัดต่อมทัยมัส, ยาสเตียรอยด์, ยาเอซาไธโอพริน, เด็ก

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