

MYASTHENIA GRAVIS IN CHILDREN AND ADOLESCENTS

A PROSPECTIVE STUDY OF TWENTY-SEVEN CASES

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SUMMARY

Myasthenia gravis (MG) is a disorder of the neuromuscular junction. In children, the disease may be congenital or due to an autoimmune process. Clinical manifestations may be purely ocular or may include generalized weakness, fatigability, dysphagia, and disorders of speech.

In this article, 27 children (14 female, 13 male) were prospectively studied from birth to age fifteen. Disease presentation was ocular in all the cases, with ptosis and diplopia. In 6 patients (all female), the disease was purely ocular, in the remaining 21, the disease was generalized. There was one case of transient neonatal myasthenia born to a myasthenic mother. Nine patients underwent thymectomy; all were reported as hyperplasia. Clinical consequences of the surgery were satisfactory. Five cases had hereditary myasthenia. In three brothers from one family, and a brother and sister from another family, disease presented from the neonatal period.

Overall, compared to adults, myasthenia seems to have a more favorable course in children. In the autoimmune form of the disease, thymectomy has a very good result. Thymoma was not observed in these cases. MG in the

newborn of myasthenic mothers had a very good prognosis, and treatment is necessary in the first few weeks only in the presence of clinical manifestations. In the congenital form of the disease, there is no indication for administration of steroids, thymectomy, or plasmapheresis.

KEYWORDS: *Myasthenia gravis, Childhood myasthenia, Congenital myasthenia, Children's neuromuscular disorders*

INTRODUCTION

Diseases of the myasthenic group are fairly uncommon in children and adolescents, and have different pathophysiological causes; in all forms, the site of the disorder is at the neuromuscular junction. The disease has several types, depending on pathogenesis and cause:

- 1) Transient neonatal MG (from myasthenic mothers, 10-15%)
- 2) Congenital myasthenia, with different pathogeneses
- 3) Generalized MG, similar to the adult form, with an autoimmune mechanism
- 4) Ocular MG, similar to the adult form

Twenty-seven children (13 boys, 14 girls) with different types of myasthenia, were prospectively studied. Disease onset was from the neonatal period in age fifteen. One of the cases was born to a myasthenic mother in myasthenic crisis. Six cases had a purely ocular form. Twenty cases had generalized MG, 10 of which started before age six; in the remaining ten, disease onset was after age six. Of the patients with generalized MG, three were brothers, and two were brother

and sister. In both of these families, the parents were closely related cousins in one family, and second cousins in the other.

All patients had a favorable response to anticholinesterase medication, such as prostigmine and neostigmine. Plasmapheresis was rarely necessary. In a four-year-old patient, Tensilon test produced respiratory embarrassment, vomiting, and consequently, aspiration pneumonia, which precipitated a myasthenic crisis, resulting in the patient's death, five days later.

MG is generally more benign in children than adults, and most children are satisfactorily controlled with anticholinesterase treatment, alone. It is important to consider congenital myasthenia if disease onset is in the first years of life. Later, acquired and autoimmune forms of the disease, in which thymectomy has excellent results, should be kept in mind. Congenital myopathies, especially myotubular myopathy, must first be ruled out. It is very important to differentiate between the acquired autoimmune

and the congenital forms of the disease. Earlier disease onset in the first years of life, absence of antibodies against acetylcholine receptor, positive family history, and similar manifestations in other family members, are all in favor of congenital MG.

Materials and Methods

All the children in which the diagnosis of MG was clinically confirmed, were included in the study with the following questionnaire:

- Age

- Sex

Age of disease onset? ... Or is it generalized?

Response to Tensilon test

Response to treatment with pyridostigmine or neostigmine

Coexistent diseases

Relation of parents

Existence of similar manifestations in siblings

History of:

- ICU admission

- Plasmapheresis

- Steroid therapy

Thymectomy, with subsequent histopathology of thymus:

The patients in whom the diagnosis was not confirmed or was dubious, were excluded from the study. Preliminary evaluation included assessment of serum muscle enzymes, thyroid function tests, serum electrolytes, and other routine tests including a chest X-ray.

One of the objectives of treatment was the performance of thymectomy in autoimmune MG, in children whose parents consented to surgery. Nine cases underwent thymectomy. Disease severity was determined by the child's ability to perform daily activities, like playing, conducting personal tasks, climbing stairs, chewing and swallowing food. Disease with only ocular manifestations was termed ocular MG; generalized myasthenia was applied to cases with weakness and fatigability of extremities, difficulty with chewing, swallowing, or speech.

If a short period of playing, sitting and standing twice, or eating a little food, produced general and respiratory signs, the disease was classified as severe; without difficulty in speech or swallowing, and if only prolonged periods of activity tired the child, the disease was classified as mild. In-between states were classified as moderate. During treatment if the response to anticholinesterases was unsatisfactory, low-dose corticosteroid (1.5-2 mg/kg) was started and later gradually tapered according to the child's state, and substituted by an alternate day regime.

Results

Of the 27 patients studied, 14 were female, and 13 male. Six cases had ocular MG, and 21 had generalized MG. Age of disease onset was from the neonatal period up to age 15. In the ocular cases, disease onset occurred only after age six.



Three brothers suffering from congenital myasthenia

Response to the edrophonium hydrochloride (Tensilon): This test was negative in one patient, and suspicious in another. In a four-year-old patient administration of Tensilon caused vomiting, respiratory difficulty, and death. In 18 generalized cases, and 6 ocular cases the test was positive.

First manifestation of disease: In 24 cases, ptosis, and then diplopia were the most common presenting manifestations of disease. In other patients, difficulty in swallowing and speech, generalized weakness, hypotonia, and ocular signs were the main clinical manifestations.

Disease severity: The generalized form of the disease was classified as severe, moderate, and mild. Seven patients had mild, 12 moderate, and

one severe disease.

Severe respiratory distress: Two cases developed severe respiratory problems during treatment, requiring ICU admission; in one case tracheotomy was needed.

Plasmapheresis: In three patients, plasmapheresis was performed; in one case with repeated crises, several courses of plasmapheresis were needed.

Thymectomy: In 9 patients, whose parents consented to thymectomy, with disease onset after six years, and after exclusion of congenital myasthenia, thymectomy was performed. The histopathology of thymus was reported to be hyperplasia in all cases. Of these 9 patients, 5 were female, and 4 were male.

No.	Age of onset	Sex	First sign	Later sign(s)	Tensilon	Response to pyridostigmine/ neostigmine
1	13 y	F	ptosis	ophthalmoplegia +diplopia	+	excellent
2	13 y	F	ptosis (right eye)	diplopia	+	good
3	13 y	F	ptosis (asymmetric)	diplopia	+	good
4	10 y	F	ptosis	diplopia	+	moderate (needed steroid therapy)
5	15 y	F	ptosis	diplopia	+	good
6	6.5 y	F	ptosis (asymmetric)	diplopia	+	good

Table 1. Ocular myasthenia

Response to anticholinesterases and othertreatment plans: Ten patients had an excellent response to anticholinesterases like pyridostigmine and neostigmine. In sixteen cases the response was moderate to good. One of the patients received 4-aminopyridine, prescribed by Dr. Newsom-Davis in England, with very good results. In eight patients we were obliged to use corticosteroids.

Family history: One brother and sister from one family and three consecutive brothers from another had congenital myasthenia. In all five patients, anticholinesterase drugs were effective.

Discussion

Myasthenia gravis is rare in children, and has different etiologies. The cases studied in this paper, were mostly referred to us from other centers. This is the first report of myasthenia gravis in children being published from Iran.

Childhood myasthenia is significantly different from the adult type. In adults, the disease is mainly autoimmune in origin, and shows a good response to thymectomy, steroid therapy, and immunosuppressive agents. In children, there are two main types of disease: the congenital form, and the autoimmune form

(similar to the adult type).

Congenital myasthenia usually starts before age six; before this age, it is less probable to encounter autoimmune MG. In 5 cases, 3 brothers and a brother and sister, the disease started at birth, with ocular manifestations, and later dysphagia. After age six, autoimmune MG is more prevalent; thymectomy has to be performed and the sooner the patient is thymectomized, the better the prognosis. It can be concluded from this study that in children with autoimmune MG, the disease severity is greater with later onset of disease. Also, thymoma seems to be very rare in children. As none of the 9 cases that underwent thymectomy, needed no medication subsequent to surgery. this indicates a better prognosis for thymectomy in children compared to adults.

One should always be cautious when performing the Tensilon test in myasthenic patients, especially in children. Rapid injection may induce respiratory arrest, and cardiac arrhythmias. The test must be performed only in the fasting condition, in a hospital setting, with resuscitation facilities and a drawn atropine syringe at hand.

In children with disease onset before age six, congenital myasthenia must be considered first. In this study, ten cases had a disease onset before the age of six (Table 3). Antibodies against acetylcholine receptors are absent in this type. A positive family history, disease onset

from the first days of life, early fatigability of the child while nursing, and absence of antibodies against acetylcholine receptors are suggestive of the congenital form of the disease. Even in these types, there is fluctuation in clinical signs, with worsening later in the day. Neostigmine (Mestinon) can be experimentally started in these patients; clinical improvement confirms the diagnosis. Congenital myopathies, especially the myotubular type that produces ocular signs, should be considered in the differential diagnosis of congenital myasthenia.

Different mechanisms are implicated in the pathogenesis of congenital MG.

- 1) Defective synthesis and storage of acetylcholine.
- 2) Reduced surface of the post-synaptic membrane, with fewer clefts in the neuromuscular junction.
- 3) Reduced amount of acetylcholine in the neuromuscular junction.
- 4) Slow closure of ionic channels by acetylcholine-slow canal syndrome.
- 5) Rapid closure of calcium channels.
- 6) Reduced number of acetylcholine vesicles.
- 7) Reduced number of acetylcholine receptors.

Ten to fifteen percent of the infants born to myasthenic mothers may have transient neonatal myasthenia with weakness of extraocular muscles, hypotonia, difficulty in nursing, and

weak cries. This is due to the transfer of maternal antibodies to the fetus, and the antigenic similarity of acetylcholine receptors in mother and the child. Diagnosis is confirmed if the signs disappear with subcutaneous injection of 0.1ml Tensilon. It is necessary to continue treatment oral Mestinon for a few weeks. One of our patients had this type of myasthenia, and showed complete recovery after two months of treatment, and needed no medication afterwards. Overall, prognosis is very good in this type of myasthenia. To avoid aspiration, it is important to insert a gastric tube in these children in the first days of life.

Conclusion

1) The only important difference between

myasthenia in the two sexes is that the ocular form is far more common in females. In the present study, all the patients with the purely ocular form were female.

2) In children, myasthenia is seen in two forms, namely congenital myasthenia and acquired autoimmune myasthenia.

3) In all types of the disease, children's myasthenia is never as severe as in adults; mortality is therefore much lower.

4) Myasthenic children rarely need ICU admission, tracheotomy, plasmapheresis, and immunosuppressive treatment.

5) Not a single case of thymoma was observed in these patients, while its prevalence is 10-15% in adult myasthenics.

No.	age of onset	Sex	First sign	Disease severity	Thymectomy	Response to treatment	Steroid therapy	Tensilon test
11	12 y	M	Diplopia	moderate	-	good	+	+
12	14 y	M	ptosis	mild to moderate	+	excellent	-	+
13	15 y	F	ptosis	mild	+	good	-	+
14	8 y	M	ptosis	mild	+	excellent	+	+
15	7 y	M	ptosis	mild	-	good	-	+
16	6.5 y	F	ptosis	moderate	+	intermediate	+	±
17	13.5 y	F	ptosis and bulbar signs	moderate	+	intermediate	+	+
18*	11 y	M	bulbar signs	severe	+	bad	+	+
19	14 y	F	bulbar signs	moderate	+	good	+	+
20	15 y	F	weakness of extremities	moderate	+	good	-	-

Table 2. Patients with generalized myasthenia, with onset after age six

* This patient had several crises, received 3 courses of plasmapheresis, and a tracheotomy.

No.	Sex	Age of Onset	First Sign	Severity	Thymectomy to treatment	Response	Steroid Therapy	Tensilon Test
1	F	3 y	ptosis	mild	-	Excellent	-	+
2	M	Neonatal	ptosis, dysphagia	moderate	-	Excellent	+	
3	M	Neonatal	ptosis, dysphagia	moderate	-	Excellent	-	+
4	M	Neonatal	ptosis,	moderate hypotonia	-	Excellent	-	+
5	F	5 y	ptosis	mild	-	Excellent	-	+
6	M	1 y	ptosis	moderate	-	Excellent	-	+
7	F	3 y	diplopia	mild	-	Intermediate	-	+
8	M	6 y	ptosis	moderate	+	Good	-	+
9	M	3 mo	dysphagia, ptosis	moderate	-	Good	-	+
10	M	1 day	hypotonia, dysphagia	moderate	-	Excellent	-	+

Table 3. Patients with generalized myasthenia; disease onset before age six

REFERENCES

6) Most patients are satisfactorily controlled with anticholinesterase treatment, alone.

7) Thymectomy has excellent results in children, and is recommended if onset is after the age of six.

8) The most common clinical manifestations of children's myasthenia are ptosis and diplopia.

9) More than 90% of the affected children have positive Tensilon test.

10) Coexistent conditions such as polymyositis and collagen vascular diseases were not observed in these patients, while in another study by the author, its prevalence was 5%.

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