Arq Neuropsiquiatr 2001;59(3-B):681-685

MYASTHENIA GRAVIS IN CHILDREN

Analysis of 18 patients

Maria da Penha A. Morita[1], Alberto A. Gabbai[1], Acary S.B. Oliveira[1], Audrey S. Penn[2]

ABSTRACT - Myasthenia gravis (MG) in childhood is rare comprising 10 to 20 % of all myasthenic patients. We studied 18 patients with MG whose first symptoms started from 1 to 12 years of age, followed at the Department of Neurology of the UNIFESP-EPM, from January 1983 to August 1997. There were 10 girls and 8 boys (1.2:1). Eleven patients (61%) presented moderate or severe generalized disease and 4 (22%) had at least one myasthenic crisis. EMG with supramaximal repetitive nerve stimulation was diagnostic in 8 (47%) out of 17 patients, and chest CT was normal in 14 patients. Seropositivity to acetylcholine receptor antibodies was found in 81.6% (9 out of 11 tested) and the levels had no relation to clinical severity. Nine out of 16 patients (56%) worsened with pyridostigmine alone and were treated with prednisone. Four out of those nine continued worsening despite steroids and were subjected to thymectomy (all showed thymic lymphoid follicular hyperplasia). Three patients (75%) improved markedly after thymectomy and one (25%) worsened, eventually getting better with intravenous immunoglobulin and oral azathioprine. MG treatment, using all resources available, has to be individualized for each child.

KEY WORDS: myasthenia gravis, child.

Miastenia gravis na infância: estudo de 18 pacientes

RESUMO - A miastenia gravis (MG) em crianças é rara e perfaz 10 a 20% dos pacientes com a doença. Relatamos 18 pacientes cujo início dos sintomas ocorreu até os 12 anos de idade, acompanhados na Disciplina de Neurologia da UNIFESP-EPM de janeiro de 1983 a agosto de 1997. Eram 10 meninas e 8 meninos (1,2:1,0). Doença generalizada moderada ou grave ocorreu em 11 crianças (61%) e 4 (22%) tiveram pelo menos uma crise miastênica. A eletroneuromiografia com estimulação repetitiva foi diagnóstica em 8 (47%) de 17 pacientes e a tomografia computadorizada do tórax não demonstrou aumento do timo em 14 pacientes. A positividade para o anticorpo anti-receptor da acetilcolina foi de 81,6% nos 11 pacientes testados e seu nível não se correlacionou com a gravidade dos sintomas. Nove dos 16 pacientes (56%) acompanhados apresentou evolução com piora tendo sido utilizada prednisona e 4 destes (25%) pioraram apesar desta terapia e foram submetidos a timectomia. Das quatro pacientes timectomizadas (todas com hiperplasia folicular linfóide do timo), 3 (75%) melhoraram e uma (25%) continuou piorando tendo sido medicada com imunoglobulina endovenosa e azatioprina. O tratamento da MG deve ser individualizado para cada criança para chegar-se o mais próximo de uma atividade de vida diária plena.

PALAVRAS-CHAVE: miastenia gravis, criança.

Myasthenia gravis (MG) in childhood and adolescence is rare comprising 10 to 20 % of all myasthenic patients[1,2]. Girls are more frequently affected than boys in a proportion of 1.3 to 1 in prepubertal ages and 1.8 to 1 in peripubertal[3,4].

The diagnosis is based essentially on the patient's history and clinical examination with a positive anticholinesterase (edrophonium or neostigmine) test[5]. EMG with repetitive stimulation and single-fiber EMG are useful for the diagnosis but technical difficulties are commonly encountered in the very young[2]. Serum acetylcholine receptor antibodies (AchRAb) are important to confirm the diagnosis but are more frequently negative when compared to adults. Antibody-negative myasthenic children are not rare[2-4].

Treatment of myasthenic children (as in adults) is based on one or more of the following: anticholinesterase drugs, immunosuppressants (mainly prednisone

[1]Department of Neurology of the Universidade Federal de São Paulo, Escola Paulista de Medicina (UNIFESP-EPM), São Paulo SP, Brazil; [2]Department of Neurology of the Columbia University, New York, NY, USA. Maria da Penha A. Morita is presently at the Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto SP, Brasil, and Audrey S. Penn at the NIH, Bethesda, MD, USA.

Received 8 March 2001, received in final form 19 June 2001. Accepted 22 June 2001.

Dr. Alberto A. Gabbai - Departamento de Neurologia - UNIFESP-EPM- Rua Botucatu 740 – 04023-900 São Paulo SP - Brasil.

and azathioprine), plasmapheresis, intravenous high-dose immunoglobulins (IVIg), and thymectomy[5]. Treatment choices are nonetheless not easy due to the rarity of the disease, concern over long term deleterious effects in early ages of steroids, immunosuppressants[6], and thymectomy[7], and a false belief that in childhood there is a high spontaneous remission rate[4,8].

Due to the scarcity of data on myasthenic children in the Brazilian literature[9-11], we present herein the clinical profile, diagnosis, management and follow-up of prepubertal children with MG seen at the Department of Neurology of the UNIFESP-Escola Paulista de Medicina.

METHOD

We studied 18 patients (approved by the Ethics Committee of our Institution), whose symptoms started between 1 and 12 years of age (mean 7.3; median 9), diagnosed with myasthenia gravis[5], from January 1983 to August 1997. We excluded patients with a family history of myasthenia gravis or those with parental consanguinity. The follow-up period varied from 0 to 108 months (mean 44.9; median 48). We used Osserman & Genkins[12] classification to characterize the clinical forms. We also used a clinical severity follow-up classification in which signs and symptoms were divided into ocular (O), bulbar (B) and generalized (G). Generalized and bulbar signs and symptoms were subdivided in light (L), moderate (M) and severe (S). A light symptom existed when complained but not found upon examination or when there was post-exercise fatigability; moderate was when there was muscular weakness up to 4 on the manual muscle test (MMT)[13]; and severe when weakness was 3 or less on the MMT.

All 18 patients underwent at least one neurological examination. Seventeen patients were subjected to an EMG with repetitive nerve stimulation[2] and 12 to a pharmacological test with neostigmine[5]. Chest CT scan was done in 14 patients. AChRAb titles were determined by radioimmunoassay in 11 patients. Titles were assayed either at the Specialty Labs in Santa Monica, CA, or the Columbia University, NY.

Thyroid function tests and screening for collagen-vascular diseases were obtained in 14 patients.

RESULTS

Sex and age of onset - There were 10 girls and 8 boys (1.2:1.0). Symptoms started before 9 years of age in 7 patients and between 9 and 12 in 11.

Initial symptoms and signs - Seventeen patients (94.4%) had ptosis as one of the initial symptoms. Ptosis was bilateral in 15 patients (88%) and unilateral in 2 (12%). Diplopia was present in 11 patients (61%), bulbar signs in 9 (50%), facial weakness in 10 (55%) and limb weakness in 12 (66.6%).

Clinical classification - There were 4 patients with the ocular form of the disease and 14 with the generalized. Out of the 14 patients with generalized MG, 9 (64.2%) had moderate or severe disease. Four of those (44.4%, or 22.2% of total) had at least one myasthenic crisis during the entire follow-up period.

Diagnostic tests - The pharmacological test with neostigmine sulphate was positive in all 12 patients tested. EMG with supramaximal repetitive nerve stimulation was diagnostic in 8 (47%) out of the 17 patients tested. In those who had normal repetitive stimulation and generalized disease, generalized disease was always light. AChRAb was determined in 11 patients and was positive in 7 (63%). By the time of assessment, 5 were classified as 2A, 3 as 2B, 2 as 3, and 1 as 4. More than one determination was possible in 7 patients with a total of 26, yielding 2 additional positive results (9 patients or 81.8% of those tested). We did not find any correlation between the severity of disease and AChRAb levels. (Table 1). Chest CT was normal in all 14 patients tested. Thirteen of the 14 patients tested had normal thyroid function tests. One had hypothyroidism. Out of 14 patients screened for collagen vascular diseases, 2 had low serum complement levels and 1 had positive antinuclear antibodies with no clinical evidence of disease.

Treatment - Treatment and follow-up data were available for 16 of the 18 patients. Two patients were lost to follow-up after the first consultation. Therapeutic management followed the same rationale for all patients. First we used anticholinesterase drugs as needed to improve the symptoms. Those who could not cope with the daily chores or worsened even with the maximum anticholinesterase tolerated doses and those who had a myasthenic crisis, were started on prednisone. Those who worsened on prednisone were subjected to thymectomy. The clinical severity status dictated therapy, and there was no minimum time frame followed for each treatment before we introduced the next. One patient worsened even after thymectomy and was treated with azathioprine and IVIg (see below).

Anticholinesterase drugs - All patients were treated with oral doses of pyridostigmine bromide, 30 to 300 mg per day. Two patients (12.5%) had a complete remission in 1 to 3 months, 3 patients (18.7%) improved, 2 patients (12.5%) remained the same, and 9 (56.2%) worsened.

Prednisone - Nine patients took at least 1 mg/kg/day of oral prednisone. Four (44.4%) improved, 1

Table 1. AchRAb found in 11 children with MG.

Patient		Classification		C	T	AchRAb titles (nmol/l)
		Clinic	PhEx			
FRSS		2B	OG (M)	N	N	54,9 (+)
DPM	(d1)	2A	O	N	N	4,8 (+)
	(d2)		O	Y	N	6,9 (+)
	(d3)		O	Y	N	**4,5(+)
MLF	(d1)	4	OB(S) G(M)	Y	N	*4,2 (+)
	(d2)		Normal	N	Y	3,8 (+)
ANS	(d1)	3	Normal	N	N	*< 0,8 (-)
	(d2)		OB(S) G(S)	Y	N	*< 0,8 (-)
	(d3)		Normal	Y	Y	1,1 (-)
	(d4)		Normal	Y	Y	2,7 (+)
	(d5)		Normal	Y	Y	**1,0 (-)
JDS		2A	G(M)	N	N	19,8 (+)
DM	(d1)	2A	OB(L) G(L)	N	N	(+)
	(d2)		O	N	N	1,3 (-)
	(d3)		O	N	N	2,8 (+)
	(d4)		O	N	N	**0,7 (-)
JCA		2B	G(L)	Y	N	3,0 (+)
RFCC	(d1)	2A	OB(L) G(S)	N	N	*< 0,8 (-)
	(d2)		OB(L) G(M)	Y	N	*< 0,8 (-)
	(d3)		O	Y	N	0 (-)
	(d4)		O	Y	N	**0 (-)
JCS	(d1)	2B	O	N	N	1,9 (-)
	(d2)		O	N	N	**1,2 (+)
MCAS	(d1)	3	OB(S) G(S)	Y	N	9,6 (+)
	(d2)		OB(S) G(M)	Y	Y	**6,0 (+)
VBS		2A	O	N	N	**0,5 (-)

(d1,2,3 or 4), number of determinations; Clinic, clinical classification (Osserman & Genkins)[12]; PhEx, physical examination; C, corticosteroids; T, thymectomy; Y, yes; N, no; *, done at the Specialty Laboratories - Santa Mônica, CA (normal < 0,8 nmoles/l). Obs.: all other determinations were done at the Presbiterian Medical Center, Columbia University, New York, NY by one of the authors, ASP. (normal < 2,7 nmoles/l); **, normal < 1.0 nmol/l.

Table 2. Analysis of 4 children with myasthenia gravis post-thymectomy.

Patient	Age at first symptoms in years	Age at surgery in years	Follow-up in months	Status post-surgery	Drugs used
MLF	9	11	59	A	Py
ANS	3	6	56	W/I	Py+Pr
MCAS	11	12	36	W	Py+Pr or Py+Az or IVIg
MBS	9	9	33	A	Py

A, asymptomatic; Az, azathioprine; I, improvement; IVIg, intravenous immunoglobulin; Py, pyridostigmine bromide; Pr, prednisone; W, worsening.

(11.1%) remained the same and 4 (44.4%) worsened. Those latter were subjected to thymectomy.

Thymectomy - Four girls who continued worsening even taking anticholinesterase drugs and prednisone were subjected to transsternal thymectomy. There were no operative complications. In all patients histopathology showed thymic lymphoid follicular hyperplasia. Follow-up post-thymectomy varied from 33 to 59 months. (Table 2).

One of the 4 patients was asymptomatic, taking no drugs, 59 months after thymectomy. Another patient had worsening periods during the 56 months of post-thymectomy follow-up. She would improve with increasing doses of prednisone and pyridostigmine. After improvement, doses were tapered down and she would remain well for another period of time. Worsening periods were less frequent after the second year post-thymectomy. Another patient worsened despite increasing doses of prednisone. She was started on azathioprine with improvement for 2 years. Azathioprine had to be discontinued due to severe leukopenia and the patient worsened again. She was started on 400 mg/kg/day of IVIg for 5 consecutive days, once every 6 weeks and was asymptomatic at the last follow-up, 36 months post-thymectomy. Another patient was asymptomatic with decreasing doses of pyridostigmine 33 months post-thymectomy. Three patients out of 4 (75%) improved after thymectomy (Table 2).

DISCUSSION

We have found, like others[4,14] that autoimmune MG in children is not a benign disease. Eleven of our 18 patients (61%) presented severe or moderate generalized MG, and 4 (22%) had at least one myasthenic crisis.

The anticholinesterase diagnostic test was useful in our patients. We used neostigmine that showed a positivity similar to the traditional Tensilon test[2,15,16]. We found the longer action of neostigmine somewhat advantageous since we had more time to observe the positive signs, especially in the very young.

EMG repetitive stimulation was useful in the diagnosis of our patients but, like others we found that its sensitivity correlated with the form and severity of the disease – it is low in the ocular forms, increases in the generalized forms and is even higher the more severe the disease is manifested[17-19].

Eighty-seven percent of our abnormal repetitive stimulation tests was in patients with generalized MG and the percentage of abnormal tests was even higher when the patient had muscle weakness by the time of the examination. It is possible that in a few of our young patients, constant crying and agitation during the exam may have hampered its proper interpretation.

A positive AchRAb assay is important to confirm autoimmune MG in children, but a negative test does not rule it out[20-23]. As a matter of fact seronegative MG is common in children specially in prepubertal ages[2,4,5]. It is possible that the seronegativity be due to the obvious hormonal and immunological immaturity at that age or also to the different antigenic characteristics of the immature AchR[3,23]. At first, 7 out of 11 of our patients (63%) tested positive, but with additional testing we increased our positivity to 82%. Like others[3], we have found that it is important to retest negative patients as they get older in order to ascertain the diagnosis and rule out a congenital MG (CMG). In CMG the AchRAb is always negative and there is no role for immunosuppressive treatment[5]. We have also found that the AchRAb titers did not correlate with the severity of the disease. Like others[24-26], we may speculate that lower AchRAb titers in more severely affected patients may simply reflect their more aggressive immunosuppressive treatments.

We treated our patients according to the severity of the disease, seeking a complete resolution of the symptoms. We started all patients on oral pyridostigmine and considered as a spontaneous remission the 2 patients (12.5%) who remitted on that drug alone. That is a low spontaneous remission rate, but in accordance with others[4,8,14]. Also on pyridostigmine alone, 3 patients improved (18.7%), and 2 (12.5%) had their symptoms stabilized. The 9 remaining patients were treated with oral prednisone. No patient remitted on that drug but 5 (56%) were stable enough as not to need further treatments. During the course of prednisone we aimed at the lowest effective alternate-day dose in order to minimize the well known deleterious effects of long term steroids in children[27]. Due to continuous clinical worsening and myasthenic crises, four of the 9 patients who were taking prednisone were subjected to transsternal thymectomy.

Although lacking major evidences for efficacy[28], thymectomy is a well-accepted treatment for children with MG[1,2,5,7,8,29]. Two (50%) of our 4 patients thymectomized had a marked improvement followed by remission. One (25%) continued to have worsening periods but those were less frequent and severe as compared to the pre-thymectomy period. She did

not have any further myasthenic crisis after thymectomy. One patient continued to deteriorate, with myasthenic crises even after thymectomy. Upon the last follow-up she had just finished one course of IVIg with marked improvement, and was on azathioprine. IVIg seems to be effective for short-term management of children with MG, specially for thymectomy preparation and for improvement in acute clinical deteriorations[30]. When using IVIg, another long-term immunosuppressive treatment has to be used, as we did with our patient. Out of the few options (azathioprine, ciclophosphamide, cyclosporine) we chose azathioprine for its efficacy and safety. There is a very low risk for developing cancer in patients taking azathioprine for up to 20 years[31,32].

If we consider the high post-thymectomy remission rates already published [7], and that 75% of our patients improved with thymectomy with no surgical morbidity, and if we take into account the long-term morbidity of steroid use in children[33], it seems reasonable to offer early thymectomy for severely affected children with MG[34]. Moreover, the risk of post-thymectomy immune deficiency or cancer in children seems to be negligible[7].

There is still no effective, disease-specific and low-toxicity immunomodulatory treatment for MG. Treatment has to be individualized for each patient, using all resources available, aiming at least to sufficient improvement to enable a full and active lifestyle.

REFERENCES

1. Szorbor A, Máttyus A, Molnár J. Myasthenia gravis in childhood and adolescence: report on 209 patients and review of literature. Acta Paediatr Hung 1988-1989;29:299-312.
2. Snead OC, Benton JW, Dwyer D, et. al. Juvenile myasthenia gravis. Neurology 1980;30:732-739.
3. Andrew PI, Massey JM, Sanders DB. Acetylcholine receptor antibodies in juvenile myasthenia gravis. Neurology 1993;43:977-982.
4. Evoli A, Batocchi AP, Bartoccioni E, Lino MM, Minisci C, Tonali P. Juvenile myasthenia gravis with prepubertal onset. Neuromuscul Disord 1998;8:561-567.
5. Swaiman KF. Diseases of the neuromuscular junction. In Swaiman KF (ed.) Pediatric neurology. 2.Ed. Saint Louis: Mosby, 1994:1453-1476.
6. Evoli A, Batocchi AP, Tonali P, Marciano M. Risk of cancer in patients with myasthenia gravis. Ann N Y Acad Sci 1998;841:742-745.
7. Seybold ME. Thymectomy in childhood myasthenia gravis. Ann N Y Acad Sci 1998;841:731-741.
8. Rodriguez M, Gomez MR, Haward FM Jr, et al. Myasthenia gravis in children: long-term follow-up. Ann Neurol 1983;13: 504-510.
9. Lopes JR, Fontenele FA. Infantile myasthenia gravis: report of a case diagnosed clinically. Arq Neuropsiquiatr 1985;43:316-318.
10. Assis JL, Marchiori PE, Zambon AA, Scaff M. Juvenile myasthenia gravis and thymectomy: report of ten cases. Rev Hosp Clin Fac Med Sao Paulo 1992;47:234-236.
11. Cunha FM, Scola RH, Werneck LC. Myasthenia Gravis. Clinical evaluation of 153 patients. Arq Neuropsiquiatr 1999;57:457-464
12. Osserman KE, Genkins G. Studies in myasthenia gravis: a review of a twent-year experience in over 1200 patients. Mt Sinai J Med 1971;38:497-537.
13. AIDS to examination of peripheral nervous system. London: Ballière Tindall, 1986, 61 p.
14. Millichap JG, Dodge PR. Diagnosis and treatment of myasthenia gravis in infancy, childhood and adolescence: a study of 51 patients. Neurology 1960;10:1007-1014.
15. Batocchi AP, Evoli A, Palmisani MT, et al. Early-onset myasthenia gravis: clinical characteristics and response to therapy. Eur J Pediatr 1990;150:66-68.
16. Roach ES, Buono G, Mclean Jr W, Weaver Jr G. Early onset myasthenia gravis. J Pediatr 1986;108:193-197.
17. Seybold ME, Haward Jr FM, Duane DD, et al. Thymectomy in juvenile myasthenia gravis. Arch. Neurol 1971;25:385-392.
18. Horowitz SH, Genkins G, Kornfeld P, Paparestas AE. Eletrophysiologic diagnosis of myasthenia gravis and the regional curare test. Neurology 1976;26:410-417.
19. Oh SJ, Eslami N, Nishihira T, et. al. Electrophysiological and clinical correlation in myasthenia gravis. Ann Neurol 1982;12:348-354.
20. Sano M, Lambert EH, Mccormick DJ, Lennon VA. Muscle acetylcholine receptors complexed with autologous IgG reflect seropositivity but not necessarialy in vivo binding. Neurology 1992;42:218-222.
21. Newson-Davis J. Myasthenia gravis and myasthenic syndromes: autoimmune disease at the neuromuscular junction. Curr Opin Neurol Neurosurg 1991;4:683-688.
22. Yamamoto T, Vincent A, Ciulla TA, et al. Seronegative myasthenia gravis: a plasma factor inhibiting agonist-induced acetylcholine receptor function copurifies with IgM. Ann Neurol 1991;30:550-557.
23. Mishina M, Takai T, Imoto K, et. al. Molecular distinction between fetal and adult forms of muscle acetylcholine receptor. Nature 1986;321:406-411.
24. Komiya T, Sato T. Long-term follow-up study of relapse in symptoms and reelevation of acetylcholine receptor antibody titers in patients with myasthenia gravis. Ann NY Acad Sci 1988;540:605-607.
25. Limburg PC, The TH, Tappel EH, et al. Anti-acetylcholine receptor antibodies in myasthenia gravis: relation to clinical parameters in 250 patients. J Neurol Sci 1983;58:357-370.
26. Oosterhius HJGH, Limburg PC, Tappel EH, et al. Anti-acetylcholine receptor antibodies in myasthenia gravis: clinical and serological follow-up of individual patients. J Neurol Sci 1983;58:371-385.
27. Lettgen B. Influence of steroid medication on bone mineral density in children with nephrotic syndrome. Pediatr Nephrol 1994;8:667-670.
28. Gronseth GS, Barohn RJ. Practice parameter: Thymectomy for autoimmune myasthenia gravis (an evidence-based review). Neurology 2000;55:7-15.
29. Assis JL. Imunopatologia do timo. In Assis JL (ed.) Miastenia grave. São Paulo: Savier 1990:105-120.
30. Selcen D, Dabrowski ER, Michon AM, Nigro MA. High-dose intravenous immunoglobulin therapy in juvenile myasthenia gravis. Pediatr Neurol 2000;22:40-43.
31. Silman AJ, Petrie J, Hazleman B, Evans SJ. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow-up study. Ann Rheum Dis 1988;47:988-992.
32. Confavreux C, Saddier P, Grimaud J, Moreau T, Adeleine P, Aimard G. Risk of cancer from azathioprine therapy in multiple sclerosis: a case-control study. Neurology 1996;46:1607-1612.
33. Kerribijn KF, De Kroon JPM. Effect on height of corticosteroid therapy in asthmatic children. Arch Dis Child 1968;63:484-490.
34. Andrews PI. A treatment algorithm for autoimmune myasthenia gravis in children. Ann N Y Acad Sci 1998;841:789-802.