Article
Arq Neuropsiquiatr 2010;68(6):843-848

Myasthenia gravis in Ceará, Brazil

Clinical and epidemiological aspects

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ABSTRACT

A retrospective chart review was performed on patients diagnosed as having myasthenia gravis in Ceará State, Brazil and who were followed from October 1981 to June 2009. Clinical and epidemiologic aspects were evaluated. In this work, 122 patients were studied, of whom 85 (69.7%) were females and 37 (30.3%) were males. The disease duration ranged from five months to 50 years (8.9±8.1 years). Age at the first symptoms varied from 0 to 74 years (31.9±14.4 years). The first main symptoms and signs were ptosis, diplopia and limb weakness. Generalized myasthenia was the most common clinical presentation, but 5.1% (n=6) persisted as ocular myasthenia. Thymectomy was performed in 42.6% (n=52) of myasthenic patients. A thymoma was present in 10 patients. Serum acetylcholine receptor (AChR) antibodies were present in 80% (n=20) of specimens tested. The data presented are similar to those of studies performed in other countries.

Key words: myasthenia gravis, clinical evaluation, epidemiology.

Miastenia gravis no Ceará, Brasil: aspectos clínicos e epidemiológicos

RESUMO

Foram analisados, retrospectivamente, os prontuários de pacientes miastênicos, diagnosticados e seguidos entre outubro de 1981 e junho de 2009 no Estado do Ceará, Brasil. Foram coletados dados clínicos e epidemiológicos. Na casuística foram estudados 122 pacientes: 85 (69,7%) do sexo feminino e 37 (30,3%) do sexo masculino. O tempo de doença variou de 5 meses a 50 anos (8,9±8,1 anos). A idade de inicio da doença variou de 0 a 74 anos (31,9±14,4 anos). Na amostra estudada, os primeiros sintomas foram principalmente ptose, diplopia e fraqueza dos membros. A maioria dos pacientes apresentou a forma generalizada, enquanto 5,1% (n= 6) persistiram com miastenia ocular. Timectomia foi realizada em 42,6% (n=52) dos pacientes. Timoma estava presente em 10 pacientes. Anticorpo anti-receptor de acetilcolina foi positivo em 80% (n=20) das amostras testadas. Os aspectos clínicos e epidemiológicos da amostra estudada têm semelhança com aqueles estudados em outros países.

Palavras-chave: miastenia grave, avaliação clínica, epidemiologia.

Myasthenia gravis (MG) is a potentially serious but treatable autoimmune disease affecting the neuromuscular junction, whose main clinical feature is fluctuating weakness and fatigability of the voluntary muscles[1-5]. The weakness tends to increase over the day or with continued activity, and the condition improves with rest or after the administration of anticholinesterase drugs[4, 6].

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Received 4 December 2009
Received in final form 1 June 2010
Accepted 8 June 2010

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Several forms and causes of MG have been described, such as an acquired autoimmune form, a neonatal form and familial or sporadic congenital myasthenic syndromes. The first is caused by antibody-mediated autoimmune attack directed against nicotinic acetylcholine receptors on the postsynaptic membrane of the neuromuscular junction[2,4]. Congenital myasthenic syndromes form a heterogeneous group of genetic diseases characterized by a dysfunction of neuromuscular transmission[7], and transitory neonatal myasthenia is a self-limited disorder that follows the passive transfer of maternal antibodies to the fetus[8]. MG has also been categorized into subtypes according to age at onset (early versus late), forms (purely ocular or generalized), presence or absence of acetylcholine receptor (AChR) antibodies in serum and associated thymoma[9].

MG is a rare disease. Its incidence varies with age, gender and ethnic group[10]. It is thought to be more common in young women and older men[10]. The annual incidence of myasthenia has been reported to be in the range of 1 to 15/million; the point prevalence rate ranges from 3 to 175/million and has increased from the 1950s to the 1990s[6,11]. The disease has a higher prevalence in women than in men, with an approximate female-to-male ratio of 2:1[12]. MG in childhood and adolescence is rare[13,14]. Girls are more frequently affected than boys in a proportion of 1.3:1 at pre-pubertal ages and 1.8:1 in peripubertal ages[15]. Without treatment, 20-30% of patients will die in 10 years[8], but with appropriate therapy, most patients are able to live productively.

In Brazil, there are relatively limited data on the occurrence of MG and its clinical and epidemiological aspects (Table 1)[5,14,16]. There have been no reported studies of MG in Northeast Brazil.

The aim of the present study was to explore the clinical and epidemiological aspects of MG gravis in a sample of Brazilian patients under care in Ceará, Brazil. The present data are compared with those obtained from other studies reported in the medical literature.

METHOD

A retrospective study was performed on patients with MG. Data were obtained from the charts of patients seen from October 1981 to June 2009 at the Neurology Service of Hospital Universitário Walter Cantídio and Hospital Geral de Fortaleza, Fortaleza, Ceará, Brazil. Other neurology departments, practicing neurologists and the Associação Cearense de Miastênicos were contacted to find other myasthenic patients who had not been treated in one of the two centers. The present study was approved by the ethics committee of Hospital Universitário Walter Cantidio and Hospital Geral de Fortaleza. A standardized questionnaire was filled out by one of the authors of the present study.

Each patient record was carefully reviewed for the accuracy of diagnosis. The diagnosis of myasthenia was based on three or more of the following criteria: typical history; clinical evidence of fatigability with recovery on rest; clinical response to anticholinesterase administration; detection of acetylcholine receptor antibodies; decrease in electrical activity on repetitive nerve stimulation (RNS) and exclusion of alternative relevant diagnosis[17].

Patients who did not meet diagnostic criteria for MG or did not live in the state of Ceará at the time of admission were excluded from the analyses.

Collected data were: gender, age at first symptoms, first symptoms, development of symptoms, first neurological examination, diagnostic tests and treatment, and classification of disease at first and last clinical assessment visits.

Clinical severity of myasthenia was graded functionally according to an adaptation of a scale devised by Os-

Table 1. Descriptive epidemiologic studies of MG involving Brazilian samples.

Variable	Cunha et al. (1999)[5] N=153	Assis et al. (1999)[16] N=41	Morita et al. (2001)[13] N=18	Present study (2009) N=122
Gender				
Male	49 (32%)	24 (58.5%)	8 (44.4%)	37 (30.3%)
Female	104 (68%)	17 (41.5%)	10 (55.6%)	85 (69.7%)
Female-to-male ratio	2.1:1	0.7:1	1.2:1	2.3:1
Mean age at onset (years)	31.13	>30	7.3	31.9
First main symptom	Ptosis	No data	Ptosis	Ptosis
Thymoma	4 (2.6%)	41 (100%)	0	10 (8.2%)
Sample characteristics	Retrospective MG patients Curitiba PR, Brazil	Retrospective Thymomatous MG patients São Paulo SP, Brazil	Retrospective Myasthenic children São Paulo SP, Brazil	See methods section for details

MG: Myasthenia gravis.

Table 2. Sample characteristics according to age of onset of disease.

	Total number of patients		< 12 years		12 to 50 years		> 50 years		No data available
Variable/ Age of onset	N	%	N	%	N	%	N	%	N
Gender									
Male	37	31.6	–	–	31	30.7	6	54.5	
Female	80	68.4	5	100	70	69.3	5	45.5	5
Clinical forms									
Ocular	6	5.1	–	–	5	4.9	1	9.1	
Generalized	111	94.9	5	100	96	95.1	10	90.9	5
Osserman scale at first assessment									
0	7	6	–	–	7	7	–	–	
I	13	11.2	3	60	9	9	1	9.1	
IIA	47	40.6	1	20	39	39	7	63.6	
IIB	39	33.6	1	20	35	35	3	27.3	
III	7	6	–	–	7	7	–	–	
IV	3	2.6	–	–	3	3	–	–	6
Osserman scale at last assessment									
0	74	63.3	–	–	68	67.3	6	54.5	
I	13	11.1	2	40	8	7.9	3	27.3	
IIA	22	18.8	3	60	18	17.9	1	9.1	
IIB	8	6.8	–	–	7	6.9	1	9.1	
III	–	–	–	–	–	–	–	–	
IV	–	–	–	–	–	–	–	–	5
Acetylcholine receptor antibodies									
Positive	20	80	1	50	15	79	4	100	
Negative	5	20	1	50	4	21	–	–	93

serman and Genkins[18]: grade I involves focal disease (e.g., restricted to ocular muscles); grade II, generalized disease that is either mild (IIa) or moderate (IIb); grade III, severe generalized disease with six months of progression; and grade IV, a crisis, with life-threatening impairment of respiration.

All data were collected and stored in the Epi-Info program (version 3.5.1 for Windows). Data were analyzed with the aid of the Statistical Package for the Social Sciences (version 14.0 for Windows). Parametric data are reported as means±standard deviation (mean±SD). Frequency data are reported as percentages. Bivariate analysis was performed with Student's t-test and Fisher's exact test. χ^2 analysis was performed for non-parametric data. Differences with $p \leq 0.05$ were considered significant.

RESULTS

General socio-demographic data

Data from 122 patients, 85 (69.7%) females and 37 (30.3%) males, were evaluated. There was a 2.3:1 female-to-male ratio (χ^2; $p<0.001$). In the group with disease onset younger than 12 years old, all patients were females and two were sisters. In the group older than 50 years, there was a greater proportion of males (1.2:1), and it was more evident over 60 years, with a ratio of 1.5:1 (Table 2). Age of onset ranged 0-74 years (0-64 years in females and 15-74 years in males). The mean age at onset was 31.9±14.4 years. Age at presentation was greater in males (males 40.3±9.45, females 28.1±7.45; Student's test; $p<0.001$). Modal ages at onset varied with gender: 16 years for females and 41 years for males. Patients with thymoma were older at first symptoms compared to those without this neoplasm; only one patient was older than 50 years old, all the others were in the third and fourth decades of their lives (Table 3).

Disease duration ranged from five months to 50 years, with a mean of 8.9±8.1 years, and mean duration of follow-up was 5.8±5.9 years.

Clinical characteristics

Ocular symptoms (ptosis and diplopia) and proximal and distal limb weakness were the first main symp-

Table 3. Comparison of clinical and epidemiologic characteristics of thymomatous and non-thymomatous MG patients.

	Thymomatous		Non-thymomatous		Statistical test
Variable	N	%	N	%	p value
Gender					
Female	5	50	15	68.2	
Male	5	50	7	31.8	*
Clinical form					
Ocular	–	–	–	–	
Generalized	10	100	22	100	*
Mean age at first symptoms	37±10.9 years		27±13.1 years		Student's t p =0.04
First symptoms					
Ocular	1	10	11	50	
Oculo-bulbar	–	–	2	9.1	
Bulbar	2	20	3	13.6	
Limb weakness	3	30	4	18.2	
Generalized	4	40	2	9.1	*
Developing symptoms					
Ocular	–	–	–	–	
Oculo-bulbar	1	10	5	22.7	
Bulbar	–	–	–	–	
Limb weakness	–	–	–	–	
Generalized	9	90	17	77.3	*

*Statistical test was not performed due to inadequate power to detect differences. MG: Myasthenia gravis.

toms in all age groups, but, from 12-50 years, inability to swallow and dysphonia were frequent. In those over 50 years old, dysphonia was as frequent as diplopia. Patients with thymoma had limb weakness as the most important symptom.

At first neurological examination, oculobulbar palsies and proximal weakness of limbs were the main features in all age groups. In those patients over twelve years old, facial weakness was an important sign. Impairment of tendon reflexes, muscle atrophy and hypotonia were less common. Few patients presented with myasthenic (n=12) or cholinergic (n=1) crisis at first medical assessment.

Generalized myasthenia was the most common clinical presentation, but 5.1% (n=6) persisted as ocular myasthenia (Table 2). According to the Osserman and Genkins[18] classification, the 122 cases were distributed in all groups at first evaluation. Most of them were classified as IIA. Patients developed in a relatively benign manner, with no patients in group III or IV at last medical visit (Table 2). Patients with thymoma were classified mostly as type IIB at first assessment, but they also improved.

Serological studies were performed on 25 patients for AChR antibodies. Of those, 20 (80%) had detectable antibodies (Table 2). Repetitive nerve stimulation results were documented in 81 patients: 64 (79%) showed a decremental response, 16 (19.7%) had normal response, and one patient had a decremental response at accessory nerve and incremental response at median nerve. Fourteen (11.5%) patients were known to have undergone a Tensilon test at presentation, and in 12 (85.7%) there was a response consistent with MG diagnosis. A prostigmine test was done in 20 (16.4%) patients and found to be positive in 18 (90%).

The main diseases that were associated with myasthenia were arterial hypertension (18.8%; n=23) and diabetes (14.7%; n=18). Two patients were under investigation for systemic lupus erythematosus (SLE), six had thyroid disorders, seven had osteoporosis and two were on treatment for rheumatoid arthritis. One patient had scleroderma.

Treatment procedures

All patients were taking pyridostigmine (acetylcholinesterase inhibitor). Most of them, 109 (89.3%), used corticosteroids during phases of the disease in order to improve therapeutic response. Azathioprine was used as an adjunct to steroids in forty (32.7%) patients. Plasmapheresis and immunoglobulin was necessary in 40 (32.7%) and nine (7.4%) patients, respectively. Other immunosuppressive drugs were used for associated diseases in two cases, one being cyclosporine and the other methotrexate.

Fifty-two patients (42.6%) underwent therapeutic thymectomy. Histopathology findings were available in 32 (61.5%) cases. The most common reported histopathology findings were hyperplasia (n=16; 50%; five males and 11 females), and thymoma (n=10; 31.2%; five males and five females). Six specimens (18.8%) showed an atrophic thymus.

DISCUSSION

General socio-demographic findings

In the present study, the majority of patients were female and young. Male patients had a greater mean age of onset compared to females. Accordingly, we found a single modal age of onset of 41 years for males and 16 years for females. These data are similar to those reported by Cunha et al. who found a single peak age of onset in males between 20 and 35 years old (44.8%) and in females between 15 and 30 years old (45.2%)[5]. Christensen et al. found a greater incidence in men older than 40 years, but demonstrated a bimodal pattern with one peak consisting of females at child-bearing age and a second peak of older women[19]. Conversely, Singhal et al., in India, studied 836 patients and showed male preponderance with a ratio of 2.7:1 and a single (later) peak of males in the sixth and seventh decades[3]. Differences across studies may be in part explained by the fact that the samples vary in genetic and cultural aspects, which may affect disease expression and the access to tertiary health services, as suggested by Sighal et al [3].

It has been suggested that the prevalence of MG falls after 70 years of age[20]. Such finding is consistent with this research, where only one patient (male) was found to be older than 70. Recent population-based studies have suggested that MG has a relatively high incidence, but is under-diagnosed among the elderly[21,22]. Thus, sampling characteristics of the studies may impact such discrepant epidemiologic findings.

Childhood MG is uncommon in Europe and North America, comprising 10-15% of MG cases[23]. The onset of symptoms before 12 years of age was demonstrated in five (4.1%) patients. The lower prevalence reported in this study could be due to the fact that such patients were recruited from services that primarily deliver care to adults. This finding is in agreement with Evoli et al. who found a prevalence of juvenile myasthenia of 2.3% in the whole myasthenic population[13]. All patients in the group with such early age of onset in the present study were females. Such finding reflects that of a previous analysis of 18 patients under 12 years old, where there was a female predominance in pre-pubertal patients[14], but another study failed to show differences in gender distribution in prepubertal MG[13]. Two patients had ocular myasthenia and three the generalized form of the disease. As for disease severity in early childhood, this finding is similar to data from Evoli et al. and Morita et al. who found not only a high frequency of ocular myasthenia but also an even higher incidence of severe disease with respiratory involvement[13,14].

Clinical presentation

The first main symptoms and signs were ocular, in agreement with Robertson et al. who observed 52% of patients with ocular involvement at the beginning of disease and the more common signs and symptoms were ptosis and diplopia[17]. External ocular muscles are affected initially in around 50% of cases and eventually in 90%; in 10% of patients, these muscles are the only affected ones (ocular myasthenia)[20,24].

According to the Osserman and Genkins classification, patients were categorized into all groups at first assessment, with the majority in group IIa.[18] Coincident with Christensen et al., 43% of the patients were into this group[19]. At final neurological examination, 63.8% of all patients were asymptomatic and none were in group III or IV. Thus, the present study suggests that MG has a relatively benign course following adequate treatment.

Serological studies for AchR antibodies is specific for MG and is positive in 80-85% in generalized myasthenia and 50-60% in ocular myasthenia[20]. These data are consistent with this sample and an Indian case series[3].

Repetitive nerve stimulation is positive in virtually all cases of generalized MG but may be negative in nearly 50% of cases of the ocular form[25]. Overall, sensitivity is around 60-75%[20]. This test was employed for diagnosis in 81 patients. The majority (79.01%) displayed a characteristic decremental response.

The sensitivity of the edrophonium test is around 86% for ocular myasthenia and 95% for the generalized form[26]. It was positive in 12 (85.7%) in this series. Robertson et al. performed this test in 82 patients during clinical assessment, and 93% were found to be positive, in agreement with this study[17].

Treatment procedures

Currently, many treatment modalities for myasthenia are available: acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, plasmapheresis, intravenous immunoglobulins and thymectomy[1]. Initial treatment usually involves the use of acetylcholinesterase inhibitors, but adjuvant therapy is often needed for adequate disease control. Intravenous immunoglobulin or plasmapheresis is generally used in early stages of treatment before thymectomy, or later during an exacerbation[20].

Almost half of patients in our study sample underwent thymectomy. Rowland stated that thymectomy was a standard therapy in all the world, with no contestation

of efficacy[27]. However, to date, there have been no prospective, randomized studies to assess the effectiveness of thymectomy for non-thymomatous MG patients. In a retrospective study, Werneck et al. concluded that there was no statistical difference between conservative treatment and thymectomy groups, regarding rates of remission and/or improvement[28].

Thymic hyperplasia was the most common histopathological finding of the present study. Several reports support these findings[20,29]. Thymoma was the next most common histopathology finding. Patients with thymoma had an older age of onset of symptoms, but there were no gender differences. These data are similar to those reported by Lavrnic et al.[30].

In conclusion, the present paper reports the clinical and epidemiologic characteristics of MG in a sample from Ceará, Northeast Brazil. The findings presented here are similar to those reported in other surveys. In this sample, MG was more prevalent among young women and had a relatively benign course. Variations in findings among different studies may be explained by methodological and cultural/ethnic aspects. Further studies with different epidemiological designs (e.g., prospective and community-based) are needed to enhance our current knowledge of this complex disease.

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