Clinical profile of patients with *myasthenia gravis* followed at the University Hospital, Federal University of Minas Gerais

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Summary

Objective: to determine the clinical profile of patients with *myasthenia gravis* (MG); followed at the Neuromuscular Diseases Clinic of the University Hospital, Federal University of Minas Gerais, Brazil, and to compare it with other Brazilian case series.

Methods: sociodemographic and clinical data were collected from patients, and a systematic literature review performed, focusing on national studies on the clinical profile of MG patients.

Results: sixty nine patients were enrolled in the study. Fifty five (91%) subjects were female and the mean age (SD) was 37.6 (±11.4) years. The mean disease duration was 14.1 years. Regarding treatment, prednisone was the most used strategy (64%), followed by the use of azathioprine (43%). There was no difference between thymectomized (42) and non-thymectomized (27) patients regarding disease severity and medication use.

Conclusion: clinical and socio-demographic features of this MG sample from a University-based clinic resemble those reported in other Brazilian series and in the international literature.

Keywords: *myasthenia gravis*, epidemiology, neurology, thymectomy, therapeutics.

Introduction

Myasthenia gravis (MG) is a prototypical autoimmune disorder in which muscle weakness occurs as a result of the impairment in neuromuscular transmission.[1] The main clinical symptoms are fatigue and fluctuating weakness of ocular, bulbar, respiratory, and appendicular muscles.[2] This weakness tends to increase during the day and it is associated with physical activity, while muscle strength improves with rest or with anti-cholinesterase drugs.[3-6] In most patients, the maximum level of severity is reached during the first three years of the disease.[5-8]

For the last 60 years, several epidemiological studies have been conducted on MG worldwide with great variability in the reported prevalence and incidence of the disease. Most of these studies were done in Europe and North America.[9-16] These heterogeneous results may be partly explained by methodological differences and biological factors.[17-23] There is, for instance, hormonal and/or environmental influence on disease development.

There is no Brazilian study aiming to determine the prevalence of MG in the community. Conversely, a few Brazilian case series have been reported, describing clinical and sociodemographic features of patients followed at specialized clinics.[17-30]

The aim of the current study was to determine the clinical profile of patients with MG under treatment at the Neuromuscular Diseases Clinic of the University Hospital, Federal University of Minas Gerais (UFMG), com-

paring it with other series to draw a picture of the MG in Brazil.

Methods

This is an observational cross-sectional study that collected data from 69 patients with MG followed at the Neuromuscular Diseases Clinic of the University Hospital, UFMG. Socio-demographic and clinical information was obtained through chart review and clinical evaluation.

Diagnosis of MG was based on the following criteria: clinical history of fatigability with recovery after rest, and clinical response to the administration of anti-cholinesterase drugs, associated with antibodies detection and/or decreased electrical activity in repetitive nerve stimulation, and exclusion of alternative neurological diseases.[7,31]

The severity of MG was graded according to the *Myasthenia gravis* Foundation of America Clinical Classification (MGFA).[31] This scale was developed to identify subgroups of MG patients who share clinical features, possibly indicating similar prognosis and/or therapeutic response. It is now recognized as the main instrument to classify patients with MG, separating patients with purely ocular involvement from those with generalized or bulbar muscle weakness, specifying the degree of weakness in mild, moderate or severe.

Descriptive analysis was performed, reporting the frequency of all categorical variables, and analysis of the measures of central tendency and dispersion of continuous variables.

A systematic literature review was also carried out, selecting Brazilian studies that aimed to characterize and/or describe the clinical profile of patients with MG followed at outpatient services. The Medline and Lilacs databases were assessed. The following descriptors were used: *Myasthenia gravis* and Epidemiology; *Myasthenia gravis* and Therapeutics; *Myasthenia gravis* and Review; *Myasthenia gravis* and Prevalence, Incidence and *Myasthenia gravis*; Thymectomy and Epidemiology; Thymectomy and Therapeutics; Thymectomy and Review; Thymectomy and Prevalence, Thymectomy and Incidence. For the SciELO database, the same descriptors in Portuguese were used.

This study was approved by the Ethics Committee of the Federal University of Minas Gerais under ETIC license nº 0476.0.203.000-11.

Results

Sixty nine patients with MG were enrolled in this study (Tables 1 and 2). Most patients were women (91%) with a female:male proportion of 4:1. Mean age (SD) was 37.6 (±11.4) years. According to the MGFA, Classes II A and V had the highest number of patients, with 14 in each class (20.3%), followed by 13 patients (18.8%) in Class I.

TABLE 1 Comparison of clinical and socio-demographic characteristics of thymectomized (n=27) and non-thymectomized (n=42) patients with *myasthenia gravis*.

Data	Non--thymectomized	Thymectomized	p value
Gender			**0.22**
Female	30	25	
Male	12	2	
Age			**0.36**
18-50	31	23	
> 50	11	4	
Years of disease	14	14.2	0.55
First symptoms			**0.86**
Ocular	22	25	
Bulbar	5	6	
Generalized	5	6	
Main symptoms			**0.36**
Ocular	15	8	
Bulbar	10	11	
Generalized	13	12	
MFGA			**0.19**
I	9	4	
IIA	10	4	
IIB	2	0	
IIIA	5	7	
IIIB	3	7	
IV	6	8	
MG Composite (mean ± SD)	7.2 (4.7)	8 (5.1)	0.75
Number of crises (mean ± SD)	3 (1.2)	9 (1.6)	0.07
Treatment			**0.75**
Anticholinesterase drug	38	20	
Prednisone	22	22	
Azathioprine	14	16	
Plasmapheresis	0	1	
Other immunosuppressant	6	3	

MG: *myasthenia gravis*; MGFA: *Myasthenia gravis* Foundation of America Clinical Classification Test Statistics; Mann-Whitney U; Fischer's Exact Test.

Regarding current treatment, 30 (43%) were taking azathioprine, 9 (13%) other immunosuppressants (6 cyclophosphamide; 3 cyclosporine), 1 (1.4%) plasmapheresis,

TABLE 2 Clinical profile of *myasthenia gravis* patients from Brazilian case series.

	Study	N	F:M	Age (Mean)	Length of disease (years)	Main symptoms			Treatment				
R						O	B	G	T	I	AZA	PDN	MS
25	Oliveira et al. 1995	52	6.4:1	27	3.1	0	0	52 (100%)	52 (100%)	0	0	52 (100%)	0
17	Saraiva et al. 1996	324	2.1:1	34.6	.	62 (19.1%)	16 (4.9%)	246 (75.9%)	16 (4.9%)	.	.	.	.
18	Cunha et al. 1999	153	2.1:1	32.1	6.2	103 (67.3%)	121 (79%)	76 (49.6%)	4 (2.6%)	.	.	.	.
19	Asis et al. 1999	41	1:1.4	45	5	1 (2.4%)	6 (14.6%)	10 (24.4%)	41 (100%)	.	9 (21.5%)	21 (51.2%)	10 (24.4%)
26	Almeida et al. 2000	90	3:1	28.2	3.4	.	.	.	0	0	11 (12.2%)	0	79 (87.8%)
24	Morrita et al. 2001	18	1.2:1	7.3	.	.	.	.	5 (27.8%)	.	1 (5.6%)	16 (88.9%)	.
20	Werneck et al. 2002	24	2.3:1	39.5	4.1	0	23 (95.8%)	1 (4.1%)	12 (50%)	3 (12.5%)	4 (16.7%)	17 (70.8%)	0
27	Oda et al. 2002	22	6.3:1	37.8	7.3	.	.	.	.	.	.	.	.
28	Saito et al. 2003	21	6:1	29.7	6	.	.	.	0	.	.	.	.
21	Maffeis et al. 2004	26	2.7:1	28	.	.	.	.	18 (69.2%)	.	.	.	.
22	Ruiz et al. 2004	46	2:1	30	26.3	4 (8.7%)	22 (47.8%)	20 (43.4%)	46 (100%)	0	1 (2.1%)	7 (15.2%)	9 (19.5%)
23	Mega et al. 2005	15	2.7:1	35	.	.	.	.	15 (100%)	.	.	.	.
29	Aguiar et al. 2010	122	2.2:1	31.9	8.9	6 (4.9%)	0	111 (94.1%)	52 (42.6%)	0	40 (32.8%)	109 (89.3%)	122 (100%)
30	Lorenzoni et al. 2013	53	4.9:1	42.1	15.1	28 (52.8%)	21 (39.6%)	4 (7.5%)	21 (39.6%)	0	46 (86.7%)	50 (94.3%)	52 (98.1%)
	Current study	**69**	**4:1**	**37.6**	**14.1**	**23 (33.3%)**	**21 (30.4%)**	**25 (36.2%)**	**27 (39.1%)**	**9 (13%)**	**30 (43%)**	**44 (64%)**	**58 (84%)**

R: references; N: number of patients; F:M: female:male proportion; O: ocular; B: bulbar; G: generalized; T: thymectomy; I: immunosuppressant (except AZA); AZA: azathioprine; PDN: prednisone; SM: symptomatic medication (pyridostigmine).

44 (64%) prednisone and 58 (84%) with symptomatic drug (pyridostigmine). The use of prednisone associated with symptomatic medication was the most adopted strategy.

Despite no difference between thymectomized and non-thymectomized patients in demographic and clinical features (Table 2), all patients who underwent thymectomy reported improvement of symptoms and/or reduction of the frequency of myasthenic crises after the surgery. Two out of 27 (7.4%) had thymoma.

Socio-demographic and clinical data from the Brazilian studies are shown in Table 2. Fourteen Brazilian studies with enough data to characterize the clinical profile of MG patients were found. Only one study was carried out in children and adolescents.[24] The main clinical features are similar among the studies. Most patients were young and women. Men had a greater mean age of MG onset in comparison to women. Most patients presented ocular involvement as the first symptom, and approximately 85% of patients progressed with generalized and bulbar symptoms. Pyridostigmine was the most prescribed drug for MG, while prednisone and azathioprine were the most commonly adopted immunosuppressant strategies.

Discussion

Overall, the profile of MG patients followed at the Neuromuscular Diseases Clinic of the University Hospital, UFMG was similar to those described in other Brazilian series, which were also specialized-center based, and in the international literature.[17-30]

Ocular symptoms were the first symptoms described by most MG patients; however, they were not considered the main problem with the disease progression. Bulbar symptoms were considered the most disabling, which is in agreement with some studies.[2-4,17,18,27]

Thymectomy is mandatory in MG patients with thymoma, which was identified in two patients in the current series. For patients without thymoma, uncontrolled studies suggest that thymectomy increases the likelihood of remission. There was no significant difference between thymectomized and non-thymectomized patients in clinical parameters which is concordant with other Brazilian reports.[20,29,30] Indeed, several cross-sectional studies failed to find any significant difference between patients who underwent thymectomy and those under conservative treatment.[5,9,12,20,21,24,29] In this scenario and taking into account the risks associated with the surgical procedure, the indication of thymectomy is frequently withheld. To solve this issue a multi-center, single-blind, randomized study, comparing thymectomy to no thymectomy in MG patients receiving prednisone, is underway (clinicaltrials.gov; identifier: NCT00294658).

Only the latest studies detailed the therapeutic strategies used,[29,30] and they are concordant with the clinical practice in our clinic. In contrast, even recent Brazilian case series[18,19,22,23,25,27,29] used the clinical classification of Osserman-Gerkins, while the recommended standards of clinical research on MG and the international literature have adopted MGFA since the early 2000s.[21,30]

Conclusion

Despite the clinical heterogeneity of MG, the clinical and demographic profiles and therapeutic strategies reported in Brazilian case series are quite similar. Further studies in different settings (*i.e.* clinical *vs*. community), with long-term follow-up and collection of clinical data with standardized instruments (*e.g.* MGFA and QOLMG-15) are warranted to better define the unmet needs of the Brazilian subjects with MG.

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Resumo

Perfil clínico de pacientes com miastenia *gravis* em acompanhamento no Hospital das Clínicas, da Universidade Federal de Minas Gerais.

Objetivo: determinar o perfil clínico dos pacientes com miastenia *gravis* (MG) atendidos na Clínica de Doenças Neuromusculares do Serviço de Neurologia do Hospital das Clínicas da Universidade Federal de Minas Gerais, e comparar com outras séries de casos brasileiras.
Métodos: foram coletados dados clínicos e sociodemográficos dos pacientes, e realizada revisão sistemática de literatura, focando em estudos nacionais sobre o perfil clínico de pacientes com MG.
Resultados: sessenta e nove pacientes participaram do estudo, sendo 55 (91%) do sexo feminino, e a média de idade (desvio-padrão) de 37,6 (±11,4) anos. O tempo médio de doença foi de 14,1 anos. Em relação ao tratamento, o uso isolado de prednisona foi a estratégia mais adotada (64%), seguida do uso de azatioprina (43,3%). Não houve diferença entre os pacientes timectomizados (47) e não timectomizados (22) no que diz respeito à gravidade da doença e ao tratamento.
Conclusão: as características clínicas e sociodemográficas da presente amostra de pacientes com MG de um serviço universitário assemelham-se às características de outras séries brasileiras e da literatura internacional.

Palavras-chave: miastenia *gravis*, epidemiologia, neurologia, timectomia, terapêutica.

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