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MYASTHENIA GRAVIS AND THYMOMA

EVALUATION OF 41 PATIENTS

JOSÉ LAMARTINE DE ASSIS, ANTONIO ALBERTO ZAMBON **, PATRICIA S. SOUZA***, PAULO EURIPEDES MARCHIORI**

ABSTRACT – We evaluated the epidemiological, clinical, laboratory and therapeutical aspects of 41 patients with thymomatous myasthenia gravis. Thirty five patients (85.36%) were submitted to thymectomy. Follow-up ranged from two to 18 years. Diagnosis of thymoma was based upon clinical investigations and CT scan of the anterior mediastinum and in 11 patients supported by immunological tests of anti-striated muscle antibodies with a positive result in more than 80% of cases. Histopathologic examination of all thymomectomized patients confirmed the diagnosis of thymoma. There was a significant predominance of benign over malignant thymoma. Occurred higher prevalence of male patients and of patients over 40 years of age. The therapeutical strategy to control myasthenic clinical findings was the same as that for non-thymomatous myasthenia gravis. The corticosteroids associated to cytotoxic drugs were less often used. Radiotherapy of the anterior mediastinum was more often used in patients having invasive tumors submitted to surgery or not. With regard to survival and control of myasthenia gravis, especially in younger patients and in those submitted to early surgery, results of treatment were surprisingly favorable.

KEY WORDS: myasthenia gravis, thymoma, thymectomy.

Miastenia grave e timoma: avaliação de 41 pacientes

RESUMO – Avaliamos 41 pacientes com miastenia grave timomatosa sob os aspectos epidemiológico, clínico e terapêutico. Trinta e cinco pacientes (85,36%) foram timectomizados. O seguimento clínico variou de dois meses até 18 anos. O diagnóstico do timoma foi fundamentado no estudo de imagem do mediastino (tomografia axial computadorizada) e, em 11 pacientes, complementado com a determinação sérica de anticorpos para músculo estriado com resultado positivo em mais de 80% dos casos e confirmado pelo exame anátomo-patológico do timo realizado em todos os pacientes operados. Ocorreu predomínio significante de timomas benignos sobre timomas malignos, forma clínica generalizada severa, frequente envolvimento do sexo masculino e, em pacientes com mais de 40 anos de idade. A estratégia terapêutica para o controle dos sintomas miastênicos foi a mesma que para os pacientes não timomatosos. O emprego de imunossupressão medicamentosa esteróide associada a drogas citotóxicas foi menos frequente. A radioterapia foi usada com mais frequência nos pacientes portadores de tumores invasivos operados ou não.

PALAVRAS-CHAVE: miastenia grave, timoma, timectomia.

Acquired myasthenia gravis (MG) is an immunological disease with antibody activity against the acetylcholine nicotine receptor (antiAChR) of the neuromuscular junction, with fluctuant weakness of the skeletal muscle which improves with the administration of cholinergic drugs (CD). These antibodies are produced by B lymphocytes activated by helper T lymphocytes antigen-specific (CD4)[1,2] in the thymus and peripheral blood of patients with MG[3,4].

Neurologic Clinic of São Paulo University School of Medicine, São Paulo: *Associated Professor Neurologic Clinic; **Assistant; ***Post-graduate Student. Aceite: 9-novembro-1998.

Dr. Paulo E. Marchiori - Clínica Neurológica, Hospital das Clínicas, FMUSP - Av. Dr. Eneas C. Aguiar 255 - 01538-900 São Paulo SP – Brasil.

At the Hospital das Clinicas (General Hospital) of the Faculdade de Medicina da Universidade de São Paulo (School of Medicine of the São Paulo University - HCFMUSP) where until now about 1100 patients with MG are registered, 110 cases of thymoma submitted to surgery or not, between 1950-1995, were reviewed. In this series the association of MG and thymoma (TMG) is of 11% which agrees with references found in literature[2,4-7].

The current purpose of this work is to evaluate the epidemiological, clinical, laboratory and therapeutic survey of a 41 patients series, since 1960.

METHODS

Forty-one out of 110 TMG patients from the HCFMUSP (Table 1), were evaluated. Thirty-five patients (85.36%) underwent surgery; six (14.63%) non-thymectomized myasthenic patients received only symptomatic management with antiacetylcholinesterase drugs, and immunosuppressive agents to which, in two cases, was added X-irradiation. The evaluation of serum antiacetylcholine by radioimmunoassay and anti-striated muscle antibodies by enzymeimmunoassay (ELISA) and determination of antigen fraction of striated muscle by Western-blot were made.

Management strategy of the myasthenic symptoms in TMG was the same as that of thymoma-free MG.

There were 24 (58.53%) male and 17 (41.46%) female patients (Table 1). Upon surgery and at first examination of the nonsurgical ones, ages of patients ranged from 25 to 76 years; four (11.42%) were under 30 years old at the time of surgery, the youngest being 25 years old and with MG onset at 24. Twenty-one (60.0%) patients were over 40 years of age and one was 40 at the time of surgery (Table 1).

Table 1. Identification.

N	Name	Gender	Race (years)	Age	Age at surgery (years)	N	Name	Gender	Race (years)	Age (years)	Age at surgery (years)
1	ST	F	P	65	47	22	MRA	F	W	50	50
2	JM	M	W	57	55	23	MLAVB	F	W	49	47
3	RMA	M	Mu	38	36	24	ET	F	W	24	25
4	CRS	M	W	48	44	25	LMFR	F	W	35	35
5	AP	M	W	54	50	26	NDS	F	W	62	62
6	LDR	M	W	71	68	27	EC	M	W	70	68
7	WT	M	W	51	51	28	APM	F	W	41	40
8	VPR	M	W	76	76	29	MP	M	W	56	55
9	PH	M	W	56	52	30	AJS	M	W	39	37
10	TK	F	P	74	71	31	CJC	M	W	53	50
11	DCL	M	Mu	48	35	32	MK	M	P	63	62
12	ECR	F	Mu	56	55	33	CM	M	W	29	29
13	CRSR	M	N	39	35	34	JML	M	W	36	36
14	RVS	M	W	41	41	35	ESM	M	W	31	29
15	IS	F	W	51	47	36	IW	M	P	30	NO
16	AVI	F	P	36	28	37	MWS	M	W	30	NO
17	SRMHM	F	P	34	34	38	BASL	F	P	69	NO
18	JPC	M	Mu	62	62	39	CDC	F	W	71	NO
19	EPC	F	W	49	47	40	CRBM	F	W	74	NO
20	MP	M	W	39	39	41	MCS	F	W	65	NO
21	JBCF	M	W	28	28						

F, female; M, male; W, white; Mu, mulatto; P, pale; N, negro; NO, non operated.

Table 2. Clinical forms, histopathology, therapy, follow-up.

N	Clinical forms	Histopathology	Therapy before thymectomy	Follow-up
1*	SGF	BT	CD	SI abd CR with no drug admins (NS)
2	SGF	BT	CD + P + CLB	Drug admins. for two years post-surgery with CD + P
3	AGF	MT	CD + P	CR for two years post-surgery with DC + P; TBI, death by leukemia during the 2nd year
4*	SGF	BT*	CD + P + AZ	Poor response to sustained drug management
5	MGF	MT	CD + RT	CR, myocardial infarction at postop currently CR with CD + P
6	SGF	BT	CD + P	Currently CR with CD
7	MGF	MT	CD + P	D at post-surgery., partial removal of lung
8	SGF	MT	CD	D on 2nd post-surgery year; only performed biopsy of MT
9	MGF	BT	CD	SI sustained with CD for last four years
10	SGF	BT	CD + P	CR until now
11	AGF	MT	CD	SI sustained for 13 years
12	AGF	BT**	CD	SI until now with CD
13	SGF	BT	CD	CR sustained until now
14	SGF	BT***	CD	SI until now and drug-free
15	SGF	MT	CD + P	D one year post-surgery; CD + P maintained
16	AGF	MT	CD	D eight years post-surgery
17	SGF	BT	CD + P + PF	SI, worsening during 2nd years, DC + P + AZ with improvement until now
18	SGF	MT	CD + P	D
19	SGF	BT	CD	MG started two month post-surgery; drug-free CR from the 15th month post-surgery; contact lost after one year of CR
20	SGF	MT	CD + RT	D on 3rd day post-surgery
21	SGF	MT	CD + Cy	SI sustained for one year post-surgery; CD + EN; lost contact
22	MGF	BT	CD + RT	D on 20th day post-surgery
23	SGF	BT	CD + P	SI for two years post-surgery with DC + P; lost contact
24	SGF	BT	CD + P	CR maintained until now with CD + P
25	SGF	MT	CD + P + RT	CR sustained with DC + P until the 6th month; lost contact
26	MGF	BT	CD + P	SI at immediate post-surgery; worsening in first months; associated CLB; cardiac insufficiency, diabetes; D
27	MGF	BT	CD + P	CR with CD + P; P interrupted 2 years post-surgery; currently discreet ocular paralysis
28	SGF	MT	CD + P	Progressive worsening; went to Chl
29	MGF	MT	CD + P	CR; tumor biopsy, CR until now with CD + P
30	AGF	BT	CD + P	SI until now using DC + P + CLB
31	SGF	BT	CD + P	CR using CD until now
32	AGF	BT	CD + P	CR until now using CD + P
33	SGF	BT	CD + RT	SI using ACTH intravenous; contact lost 9 months post-surgery
34	MGF	BT	CD	D at post-surgery.
35	AGF	BT*	WACD	SI with CD + P two years post-surgery; MG developed at immediate post-surgery.
36	SGF	MT	CD + P	D at seventh month of disease; necropsy (R 92071/69 - FMUSP); MT
37	SGF	N	CD + P	ACTH intravenous; D at sixth month of disease
38	MGF	N	CD + P	CD + RT; SI maintained for five years
39	OF	N	CD + P	CR + DE + RT with SI; lost contact after two months
40	MGF	N	CD + P	CD; follow-up during 12 years with SI
41	SGF	N	CD + P	CD; lost contact on 2nd month of follow-up

SGF, severe generalized form; AGF, accentuated generalized form; MGF, mild generalized form; OF, ocular form; BT, benign thymoma; MT, malignant thymoma. * Thymoma with adjacent atrophic thymus; NS, non-specific drug administration for MG. ** Thymoma with ectopic thyroid tissue and adjacent hyperplasic thymic tissue. *** Lymph epithelium thymoma with adjacent hyperplasic thymic tissue. PF, plasmapheresis; Cy, cyclophosphamide; RT, radiotherapy; CD, cholinergic drugs; P, prednisone; AZ, azathioprine; CLB, chlorambucil; SI, significant improvement; CR, complete remission; D, death; AS, assymptomatic; NO, not operated; TBI, total body irradiation. Patients #37, #38, #40 ACT with images strongly suggesting invasive thymoma; Patient #41 had ACT showing a solid mass in the pre-vascular space; Patient #36 not defined X-ray examination and necropsy disclosed MT; DE, dexametasone; WCD, without anticholinesterasic drugs.

Tabela 3. Immunological, morphologic and histopathological data in TMG

N	Name	Anti-AChR (nM/L)	AEMA-ELISA (units)	AEMA-HEMAG (units)	ACT	Histopathology
4	CRS	71.40	98.0	13	SM	AT
5	AP	13.10	62.0	10	SM	MT
7	WT	72.50	52.0	7	SM	MT
8	VPR	81.50	65.0	10	ISM	MT
9	PH	152.00	200.0	12	ND	LET
10	TK	88.10	114.0	13	SM	LET
11	DCL	25.80	9.9	7	ND	MT
13	CRSR	110.70	88.0	11	ND	LET
15	IS	71.00	76.0	11	SM	MT
16	AVI	24.10	1.0	4	MSTB	MSTB
38	BASL	0.60	42.0	10	ISM	MT

Anti-AchR, anti-acetylcholine receptor antibody; nM, nanomol; AEMA, antibody against human muscle antigen (in units); Hemag, hemagglutination; ACT, computerized tomography of the anterior mediastinum; AT, atrophic thymus; SM, solid mass; ISM, invasive solid mass; MSTB, thymoma and lung lesions; ND, not done; T, thymoma; LET, lymph-epithelium thymoma; MT, malignant thymoma.

Among those submitted and not submitted to thymectomy, 23 (56.09%) developed severe generalized clinical form (SGF - Osserman-IV), six (14.63%) had the generalized accentuated form (AGF - Osserman-IIb), 10 (24.39%) progressed with mild generalized form (MGF - Osserman-IIa), one (2.43%) presented with the ocular form (OF - Osserman-I) and thus remained during the short term (two months) follow-up; one patient of the surgical group developed MG after thymomectomy (Case 35) (Table 2). The clinical forms that of Osserman[7] modified were adopted.

Diagnosis was mainly based on clinical examination, on the CT scans of the thorax and anatomopathologic tests of the surgical specimen of the thymus in all the thymectomized patients. A patient of the nonsurgical group (Case 36) and another of the surgical group (Case 34) were submitted to necropsy. For diagnostic support in 10 of the patients submitted to surgery and in one of the nonsurgical group (Case 38) immunologic investigations were performed: tests for the titering of antibody against human muscular antigens (AEMA)[8] and dosage of antibody against acetylcholine receptor (anti-AChR)[9]. A comparative study of the tests with the findings of the axial computerized tomography (ACT) and thymus histopathology, were undertaken (Table 3) [9]. Thymectomy was performed following the partial or total sternum-splitting approach. In one case of a very large thymoma (case 35) which invaded the right hemithorax, the chosen procedure was a posterior lateral thoracotomy.

Pathological examination of the thymus - 22 (62.85%) of patients had benign (BT) and 13 (37.14%) malignant thymoma (MT). In one patient (Case 35) tumor was large and invaded the right hemithorax. Malignancy criterion was based upon the thymoma invasiveness. In one female patient (Case 12) adjacent to the tumor ectopic thyroid tissue and hyperplasic thymic tissue were found. In one patient (Case 14) adjacent to a lymph epithelium thymoma and hyperplasic thymic tissue was found and in another patient (Case 4), besides thymoma an atrophic thymus was found.Thymomas were lymphocytic in 43%, lymphoepithelial in 29%, epithelial in 22% and spindle cells in 6%. The comparative morphological and histologic evaluation between TMG and thymomas without MG (TWMG) did not show differences.

RESULTS

In the group of 41 patients with TMG, there was a significant prevalence of males (58.5%) over females (41.4%). Prevailing age was over 30 years at MG onset, with a predominance of those over 40 years.

Severe clinical forms (Osserman-IV) prevailed in 70.73% of patients, against 24.39% of the mild forms Osserman-IIa); only one patient (Case 39) had OF (Osserman-I)and another (Case 35) presented with MG at postoperative stage.

Myasthenic crises (MC) occurred in 20% of patients submitted to surgery, in their majority (12.50%) in the immediate postoperative. In the group of patients not submitted to surgery, two (cases 36 and 37) evolved in a relatively short term to MC six and seven months after the start of myasthenic symptoms.

In the group of nonsurgical patients X-ray scans strongly suggested thymoma, except in one (Case 36) in which diagnosis was reached at by anatomopathologic results. Another patient of this group (Case 38) presented with positive immunologic assays (AEMA-ELISA and AEMA-HEMAG) for TMG, in agreement with the ACT, exhibiting a solid invasive mass.

In the 10 patients with TMG, submitted to surgery and with titers of anti-AChR, all had higher antibody levels ranging from 13.0 nM/L a 152.00 nM/L. Antibody serum levels against human skeletal muscle (AEMA-ELISA e AEMA-HEMAG) were increased in all of the patients, except in two (cases 11 and 16), whose titers were low. A variation from 1.0 to 200 units on the AEMA-ELISA and from 4 to 13 units in AEMA-HEMAG was found (Table 3).

Follow-up from two months to 18 years of 68.29% of surgical and nonsurgical patients and of 71.42% of those in the first group from two to 18 years discloses the following results for those submitted to thymectomy: 23 patients (65.70%) evolved with complete remission (CR) or significant improvement (SI); 62.85% of patients were 40 years old or more at the time of surgery and, in this subset, 60.86% evolved with SI or CR; 28.57% were not yet 40 years old and 91.66% had SI or CR; in this subset, six (60%) had MT, two (Cases 16 and 21) were under 30 years of age and one of them (Case 16) survived with short periods of SI for eight years and had pulmonary tuberculosis; in the group of those submitted to surgery with 40 years of age or more, seven (20%) had MT and only two survived: one (Case 5) has for the last five years been in CR with CD and prednisone (P); one (Case 29), solely submitted to biopsy of the tumor, has for two years been in CR with CD + P; this patient has been examined 2.5 years after surgery and is still under CR, keeping up the same therapeutic protocol.

In the group of patients not submitted to surgery two (Cases 38 and 40) had a lengthy evolution with the MGF, follow-up from five to 12 years respectively; these patients were on CD and in only one radiotherapy (RT) was used (Case 38). The female patient with OF (Case 39) had a favorable response to dexamethasone at the onset of treatment, however after a two months follow-up she did not return.

Of the group of 41 patients with TMG, 11 (26.87%) died, 25.71% of those submitted to thymectomy and 33.33% of those not submitted to surgery. In the first group, 17.14% of deaths occurred in the immediate post-surgery, while 20% died from six to eight years after surgery. In this group, five (14.28%) had MT, one (Case 26) had BT and one (Case 37) has no histologic records. Three patients with MT survived from two to eight years; one (Case 3) survived with SI for two years and died of leukemia; this patient had been submitted to immunosuppression with a variety of cytostatic drugs and total body irradiation; one (Case 16) survived for eight years and death resulted from lung multiple metastasis of MT; one (Case 8) survived for two years and death was caused by MG; only performed biopsy of MT in this case.

DISCUSSION

Although thymectomy is a very important approach to management of MG, it remains quite controversial[10,11]. However, its indication in presence of thymoma is consensual[2,6,11-14]. In an effort to lessen risks of local infiltration and to maintain CR of MG, complete excision of the tumor, of the thymic tissue and of other non vital adjacent structures is recommended in invasive thymoma, but such objectives are not always met[6,13,15-17].

In the series under study there was a significant prevalence of thymomas in the male gender and in patients with over 40 years of age. This result corresponds to the age group of patients with TMG from 50 to 60 years of age [4]. Age influenced results in the group submitted to surgery, as a higher number of patients (91.66%), under 40 years of age had favorable responses. Nevertheless, for both age groups, early surgery is of vital importance, especially in cases of invasive thymoma.

In almost all cases, thymomas come with MG, nevertheless in some there are no evident clinical findings and MG will only develop after a variable time lapse after thymectomy[2,7,18,19].

In the current series only one patient (Case 35) developed post-surgery MG. As a rule TMG develops with a severe or pronounced symptomatology and with more frequent MC, although it may evolve with mild symptoms, and seldom exhibit the ocular form[2,5]. In this series there was a significant prevalence of the severe forms (SGF and AGF) over the mild ones and only one of the OF (Case 39).

Presence of MT in the group submitted to surgery did not always shorten the survival rate or cause a worsening of MG, as 14.28% of the patients had an adequate survival with SI or CR of MG for two to five years or more.

In the current series a significant prevalence of BT over MT was found, which agrees with other authors[5,20-22], although some[13,15] have reported a high incidence of MT.

In the current paper, for the identification of thymoma malignancy, its invasiveness was adopted as the most significant factor[22]. From a histologic point of view criteria for the identification of thymoma malignancy are poor, the spreading of metastases is rare and in general takes place in the pleura and lungs[13,23,24]. In most cases thymomas start in the thymic site and exceptionally develop in an ectopic site such as the lung[23].

Diagnosis of thymomas is reached at by clinical examination and ACT supported by immunologic tests[3,5,8,9,25-33]. Using such procedures most thymomas are detected prior to surgery[21]. Immunologic assays may lead to suspect thymoma even prior to X-rays detection[3,4,8]. This is possible because of the high incidence of both antibodies anti-receptors such as anti-AChR and anti-ryanodine as well as antibodies against proteins (antigens) of skeletal muscle, in TMG[3-5,8,25-28].

Almost all of the TMG patients had autoantibodies against skeletal muscle class IgG [5,8,26]; they may be found in only 10%-15% of MG and atrophic thymus is rarely detected in patients with MG and thymic hyperplasia [5].

Antibodies against myofibrils (myosin, actin and actimyosin) are found in 85% of TMG patients [4]. In the present series, AEMA enabled to detect antibodies against skeletal muscle antigen in 11 patients and especially, when to this test was added the enzymeimmunoassay (AEMA-ELISA). A positive result was reached at in over 80% of patients. This test is highly sensitive and specific for TMG diagnosis.

Most of the authors[2,4,5,7,15,34] agree that TMG prognosis is poorer than that for non thymomatous MG. However, early surgery with total excision of tumor and current MG management protocols have partially changed such prognosis, permitting SI and even CR of MG, especially in younger patients submitted to early surgery, as this series has proven. Recurrence of thymoma is rare and does not alter prognosis[13,24]. No recurrent tumors were recorded in the present series.

Numerous efforts have been made to correlate prognosis to histopathology or with associated diseases that would be more frequent in TMG[35,36].

In conclusion, TMG has a relatively favorable prognosis with regard to the survival rate. Such prognosis depends mainly on the thymoma characteristics; if invasive or not, on its total and early excision, on MG response to treatment and to an eventual associated pathology.

In the series under study the number of patients requiring long term management with steroid immunosuppressants was significantly high. The utilization of P associated to CD led to SI or CR of the myasthenic symptomatology in most patients. Some authors[37] recommend RT in all patients with invasive thymomas and, also in those with a non excisable tumor. Others[15] use this therapeutic approach almost exclusively when the tumor has not been totally excised. Bernatz et al.[35] and Wilkins et al.[36] report a survival rates of five years in 50% and 63% respectively, with the combination of surgery-radiotherapy. Such association is considered the best treatment strategy for invasive thymomas[24].

How we did not show any differences about morphologic and histologic changes in TMG and TWMG, is possible that the development of MG can depend on the presence of protein p-153 (153 Kd) antigen in epithelial cells of cortical and well-differentiated thymomas associated myasthenia gravis[37].

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