ORIGINAL ARTICLE

THYMOMA AND MYASTHENIA GRAVIS – AN OBSERVATIONAL STUDY AT A TERTIARY CENTER

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Abstract

Introduction: *Acquired Myasthenia Gravis (MG) is a rare autoimmune neurological disorder characterized by fluctuating paresis of the skeletal muscle due to pathogenic antibodies against the acetylcholine receptor or other elements of the neuromuscular plaque. There is a close relation between MG and thymoma. We aimed to characterize a population of patients with Myasthenia Gravis associated thymoma (MGAT).*

Methods: *Retrospective and longitudinal study in all patients with MGAT observed at a tertiary center between 2009 and 2020. We assessed epidemiological, clinical, laboratory and therapeutic features of both MG and thymoma.*

Results: *We found 18 patients with an average age of 53 ± 16.2, 13 of them females. Most patients (n=15) presented the generalized MG form. Most frequent Masaoka staging was II (n=7). Regarding the WHO histopathological classification of thymoma, most patients (n=11) presented with type B2 or B3. Thirteen patients underwent extended thymectomy (12 by median sternotomy and 1 by VATS). Of the remaining 5 patients, 4 of them underwent a CT scan guided biopsy, and 1 patient did not accept further work-up. Seven patients were classified as R0 for surgical resection margins and only one of them had recurrence of thymoma. Besides surgery, oncological treatment included radiotherapy and chemotherapy. Five patients experienced a myasthenic crisis during the course of the disease. Three deaths occurred in the studied population.*

Conclusions: *This study helped to pinpoint important aspects concerning therapeutic orientation of MGAT patients, such as the clinical impact of thymectomy in the course of MGAT, the oncological prognostic value of surgical resection margins, and the importance of preoperative intravenous immunoglobulin. Management of MGAT patients is only possible with a multidisciplinary approach.*

INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune neurological disorder of the motor plate. In this condition, postsynaptic neurotransmission in the neuromuscular junction is affected by antibodies against nicotinic receptors of acetylcholine (AchR) or other proteins in the postsynaptic muscle membrane1causing fluctuating muscle weakness. Ocular weakness is the most frequent presentation but, in most patients, the disease will progress to generalized MG (gMG), affecting virtually all muscles[2].

The thymus plays an important role in the pathophysiology of MG and 75% of the MG patients demonstrate thymic abnormalities, either a germinal hyperplasia or a thymoma[2]. Thymoma is anepithelial tumor of the thymic gland.

Thymectomy should be performed in all cases of thymoma, regardless of the MG form[3,4,5,6]. Its purpose is to safely remove as much thymic tissue as possible.

We aimed to review the population of patients with the diagnosis of MGAT at our center in the last 12 years, addressing their clinical characteristics, medical and surgical treatment and follow-up throughout the years.

METHODOLOGY

This was a retrospective longitudinal study which included all patients with the diagnosis of MGAT with

treatment and follow-up at a tertiary center ---------- ---------- between 2009 and 2020. We used our center's clinical database to collect the following variables: patients' gender and age at disease onset, clinical presentation of MGAT, histological subtype according to the classification of the World Health Organization (WHO)[7], Masaoka staging[8], the classification of the Surgical Resection Margin[9], type of AChR antibodies, temporal relationship between the diagnosis of MG and thymoma, pharmacological treatment and surgical resection of thymoma, oncological treatment, therapeutic response and clinical course of both MG and thymoma.

The serologic study was performed by radioimmunoassay, the neurophysiology tests were done with repetitive nerve stimulation (RNS) at a frequency of 3 Hz, and a chest CT scan with contrast was used for the radiological diagnosis of thymoma. After biopsy orthymectomy, immunohistochemical study of the anatomical specimen was performed.

We used an Osserman's modified classification, based on the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification[10], to assess the severity of symptoms at diagnosis: Class I (patients with only ocular muscle weakness), Class II, III and IV (patients with mild, moderate and severe weakness affecting other muscles, respectively), subcategories "a" (limb and axial predominance) and "b" (oropharyngeal/ respiratory predominance), and Class V (patients with intubation needs). In addition, we stratified the progression of MG as Clinical Remission (CR) in those clinically asymptomatic under no treatment, Improved (I) in those with clinical improvement but still symptomatic (or asymptomatic but on disease-modifying drugs), Unchanged (U) for those whose symptoms showed no difference over time, Worse (W) for those whose symptoms worsened, and Died of MG (D of MG) or Died (D) whether death cause was directly or not directly related to MG, respectively.

In patients who underwent thymectomy, the oncological progression was stratified in "No recurrence" in those whose thymoma was completely removed and no recurrent disease has been notified, "Recurrence" if new lesions occurred, and "Progression" if the tumor's dimensions increased.

Furthermore, in patients who had not been through surgery, the evolution of the thymus disease was divided in "No progression" or "Progression" accordingly to the dimensions of the tumor and the occurrence of new lesions. This comparison was only made within the range of three years of follow-up from the moment of the diagnosis of the thymoma, to ensure equality.

Follow-up time ranged from 1 to 12 years. Follow up by Thoracic Surgery and Oncology included 2 visits per year with a thoracic CT in the first 2 years and then annually in case of no complications. Follow-up by Neurology was variable and tailored to the patient's needs.

We applied descriptive statistics when appropriate to analyze our data using SPSS® software, version 25 (IBM Statistics).

RESULTS

We found 18 patients, 13 of them were females (Table 1). We observed a wide range of age at disease onset (between 14 and 77 years), with an average age of 53 ± 16.2 (Figure 1).

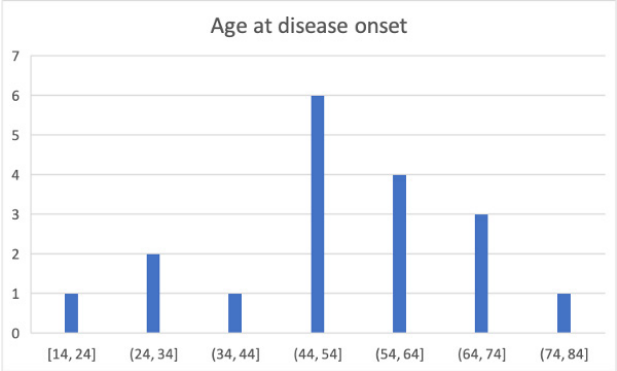

Figure 1 *Age at disease onset in years.*

Concerning the type of MG, we found 3 patients with ocular MG (Class I in the Osserman's modified classification) and 15 patients with generalized MG (2 patients at Class IIa, 2 patients at Class IIb, 1 patient at Class IIIa, 5 patients at Class IIIb, 4 patients at Class IVb and 1 patient at Class V). All patients had positive AChR antibodies. Other antibodies (such as anti-titin or anti-MUSK) were not systematically searched. Sixteen patients underwent electromyography study and all of them showed a decremental response in repetitive nerve stimulation studies.

The pharmacological treatment of MG comprised pyridostigmine in 94% of patients (n=17), corticosteroids in 89% of patients (n=16), intravenous immunoglobulin in 72% of patients (n=13) and azathioprine in 28% of patients (n=5).

Since ordering a chest CT scan at the time of a MG diagnosis is a usual practice in our Neurology department, MG diagnosis was established at the same time of the thymoma diagnosis in all but three patients. In those with delayed thymoma diagnosis, the thymoma was diagnosed two years after myasthenic symptoms' onset in two patients, and ten years after myasthenic symptoms' onset in the other patient (Table 1).

As depicted in Table 2, surgery treatment of thymoma was applied in thirteen patients with extended thymectomy, by sternotomy in twelve and by VATS in one.

Table 1

Characterization of the population of the study, regarding gender, age of onset, type of MG, severity of symptoms at diagnosis according to the MGFA clinical classification, presence of acetylcholine-receptor antibodies, results of EMG conduction studies with repetitive nerve stimulation, MG pharmacological treatment and temporal association between MG diagnosis and thymoma.

Patient ID	Gender	Age of onset	MG type	Severity of symptoms at diagnosis	AChR anti-bodies	EMG with RNS	Pharmacological treatment of MG	Temporal association between MG diagnosis and thymoma
1	Female	14	gMG	V	+	DR	P+C+IG+AZA	At diagnosis
2	Female	51	oMG	I	+	DR	P+C+IG	At diagnosis
3	Female	48	oMG	I	+	DR	P+C+IG	At diagnosis
4	Female	58	gMG	IIIb	+	DR	P+C+IG	At diagnosis
5	Female	49	gMG	IIb	+	DR	P+C+IG	At diagnosis
6	Female	60	gMG	IIa	+	DR	P+C+AZA	10 years after
7	Female	74	gMG	IIIa	+	DR	P+C+IG	At diagnosis
8	Male	42	gMG	IIb	+	DR	P+C+IG	2 years after
9	Female	74	gMG	IVb	+	No	P+C+AZA	2 years after
10	Female	48	gMG	IVb	+	DR	P+C	At diagnosis
11	Female	51	oMG	I	+	DR	IG	At diagnosis
12	Female	34	gMG	IIIb	+	DR	P+C	At diagnosis
13	Male	64	gMG	IIIb	+	DR	P+IG	At diagnosis
14	Male	46	gMG	IVb	+	DR	P+C+IG	At diagnosis
15	Male	31	gMG	IVb	+	No	P+C+IG+AZA	At diagnosis
16	Female	63	gMG	IIIb	+	DR	P+C+IG+AZA	At diagnosis
17	Male	77	gMG	IIa	+	DR	P+C+IG	At diagnosis
18	Female	72	gMG	IIIb	+	DR	P+C+IG	At diagnosis

gMG: Generalized Myasthenia Gravis. oMG: ocular Myasthenia Gravis. AChR: Acetylcholine Receptor. EMG: Electromyography. RNS: Repetitive Nerve Stimulation. DR: Decremental Response. P: Pyridostigmine. C: Corticosteroids. IG: Immunoglobulin. AZA: Azathioprine.

Four patients had an unresectable disease, and 1 refused treatment.

Seven of the operated patients also received radiotherapy (RT) and four non-operated patients received chemotherapy (CT) and RT. All these patients presented with either capsule, local, regional invasion or metastatic dissemination (stages II, III and IV of Masaoka's system). None of the stage I patients (n=4) received adjuvant treatment. The same patient who refused surgical treatment had also denied other therapeutic options.

Masaoka's staging showed 4 patients with stage I thymoma (22,2%), 7 patients in stage II (38,9%), 2 patients in stage III (11,2%), 4 patients in stage IV (22,2%), and 1 patient (5,6%) with a thymoma of unknown stage (refusal of intervention).

Pathological examination of the specimen was performed in all operated patients. Of the remaining 5 patients, 4 of them underwent a CT scan guided biopsy, and 1 patient did not accept further work-up nor surgical treatment of the thymoma. Regarding the WHO histo-

pathological classification of thymoma, 61,1% of patients (n=11) presented with type B2 (n=6) or B3 (n=5) thymomas, 11,1% with type B1 thymomas (n=2), 5,6% with type AB thymoma (n=1), 5,6% with type A thymoma (n=1). In 16,7% of patients (n=3) classification was not possible.

Patients who underwent thymectomy were classified in the surgical R, and 53,8% (n=7) were R0, 15,4% (n=2) were R1 and 30,8% (n=4) were R2.

Of all these surgical patients (n=13), twelve had a follow–up of at least 3 years. Ten of them (83,3%) had no recurrence after the thymectomy, while one patient (8,3%) recurred and one (8,3%) had progression and died.

One patient with R0 had recurrence of the thymoma, no patient with R1 had recurrence, and one patient with R2 had progression of the disease and died.

Looking at the non-surgical patients (n=5), four had a follow–up of at least 3 years. One (25%) had no progression of the oncological disease and three (75%) had progression. Of these, 2 patients died (50% of the non-surgical group).

Considering the time evolutionof deaths (n=3), the period between thymoma diagnosis and death was 1 year in two and 2 years in one patient.

About the two patients that evolved with recurrence (surgical) or progression (non-surgical), the time between thymoma diagnosis and such evolution was 3 years in both.

Concerning the MG evolution, three patients

Table 2 **Characterization of the population of the study, regarding the thymoma treatment, presence and specification of other oncological treatment, disease stage according to the Masaoka's System, histological classification according to WHO.**

Patient ID	Thymoma treatment	Other oncological treatment	Stage (Masaoka)	Histological classification (WHO)
1	ET by sternotomy	None	I	B2
2	ET by sternotomy	None	II	AB
3	ET by sternotomy	None	I	B2
4	ET by sternotomy	RT	II	B3
5	ET by sternotomy	RT	II	B2
6	ET by sternotomy	RT	III	B3
7	ET by sternotomy	RT	II	B3
8	ET by sternotomy	None	I	B3
9	Unresectable	CT + RT	IV	B2
10	Unresectable	CT + RT	IVA	B1
11	ET by sternotomy	RT	III	B3
12	ET by sternotomy	RT	IIA	B2
13	ET by sternotomy	None	I	B1
14	Unresectable	CT + RT	IVA	Unclassified
15	Unresectable	CT + RT	IVA	Unclassified
16	ET by VATS	None	IIA	A
17	Denied treatment	None	Unknown	Unknown
18	ET by sternotomy	RT	IIA	B2

ET: Extended Thymectomy. VATS: Video Assisted Thoracic Surgery.RT: Radiotherapy. CT: Chemotherapy. WHO: World Health Organization.

Table 3 **Characterization of the population, divided accordingly to the surgical (with surgical resection margin) or non-surgical treatment and progression of oncological disease.**

SURGICAL PATIENTS			NON-SURGICAL PATIENTS	
ID	Surgical Resection Margin	Progression of Oncological Disease	ID	Progression of Oncological Disease
1	0	No recurrence	9	Progression (and D)
2	0	No recurrence	10	Progression (and D of MG)
3	0	No recurrence	14	Progression
4	0	No recurrence	15	No progression*
5	2	No recurrence	17	No progression
6	2	Progression (and D)		
7	2	No recurrence		
8	0	No recurrence		
11	2	No recurrence		
12	0	Recurrence		
13	0	No recurrence		
16	1	No recurrence*		
18	1	No recurrence		

D: died. D of MG: died of MG.
* - patients with less than 3 years of follow-up time.

(16,7%) achieved clinical remission of MG, eleven patients (61,1%) had their neuromuscular disease improved, while only three (16,7%) had gotten worse, and one (5,6%) died of this disease.

As previously noted, thirteen patients underwent thymectomy (72,2%). Of those, only 30,8% (n=4) did not receive intravenous human immunoglobulin the month before surgery, although only one patient has developed a myasthenic crisis during postoperative period.

In fact, 27.8% of patients (n=5) experienced a myasthenic crisis somewhat during the course of the disease. All of them had gMG, with Masaoka stages ranging from I to IV.

Moreover, 22.2% of patients (n=4) presented diaphragm elevation, whether from the surgical resection or from the radiotherapy sessions: three of them on the left diaphragm, and one on the right.

Three deaths occurred in the studied population. Two did not undergo thymectomy due to unresectable thymoma and received radiotherapy and chemotherapy. In two of them, the death cause was directly related to thymoma invasion with massive pleural effusion and / or vena cava thrombosis. In the other patient, death was directly related to MG with respiratory failure (D of MG).

DISCUSSION

MG diagnosis is based on patient's symptoms and typical findings on neurological examination. MGAT may present either with generalized or ocular MG forms and disease manifestations are variable[11]. Although thymoma typically occurs in the fourth and fifth decades of life with no gender difference[12], we found a female preponderance, which can be explained by the small size of our sample.

Generalized onset of MGAT predominates in our sample, which is in line with the available literature11. Besides, oropharyngeal and respiratory symptoms (subcategories "b") also predominate over axial and limbs' involvement (subcategories "a") [2].

All patients had positive AChR antibodies, which is a known feature of patients with MGAT[11]. All but two patients underwent electromyographical study with re-

Table 4 **Characterization of the population of the study, regarding the progression of MG, pre-operative IV IG protocol, an event of a myasthenic crisis, adverse effects of the treatment and the occurrence of death.**

Patient ID	Progression of MG	Preoperative IV IG	Myasthenic crisis	Adverse effects of the treatment	Death
1	I	Yes	Yes	No	No
2	CR	Yes	No	No	No
3	I	Yes	No	ED	No
4	I	No	No	No	No
5	I	No	No	No	No
6	I	No	Yes	ED	Yes
7	W	No	No	ED	No
8	I	Yes	No	No	No
9	I	-	No	-	Yes
10	D of MG	-	No	-	Yes
11	CR	Yes	No	ED	No
12	W	Yes	No	No	No
13	I	Yes	Yes	No	No
14	I	-	Yes	-	No
15	I	-	Yes	-	No
16	I	Yes	No	No	No
17	CR	-	No	-	No
18	W	Yes	No	No	No

MG: Myasthenia Gravis. CR: Clinical Remission. I: Improved. W: Worse. D of MG: Died of MG. IV IG: Intravenous Immunoglobulin. ED: Elevated Diaphragm.

petitive nerve stimulation. EMG showed a decremental response (DR) in all of them. EMG was not performed in two patients due to therapeutic urgency and typical clinical features.

MGAT diagnosis needs demonstration of a thymoma, for which a contrast-enhanced chest CT is useful showing the local and regional extent of the neoplasm. Although chest MRI helps to better outline soft tissue and to establish the surgical plan, CT and anti-titin or anti-rynodine antibodies assay (MGAT specific antibodies not routinely assessed) have the same sensitivity for the diagnosis of thymoma[13]. In our sample, thymoma detection was established with chest CT following MG diagnosis in all patients.

Although not devoid of risks, thymectomy has evolved through the years and has become a safe procedure for patients with MGAT. It has many different surgical approaches, such as transcervical, minimally invasive, and transsternal[3]. In our sample, the majority of patients with surgical treatment underwent transsternal extended thymectomy.

As previously noted, thymectomy should be performed in all cases of MGAT, regardless of the MG form[3,4,5,6]. Highest success rates (80%) are achieved with radical resections of the entire cervical and mediastinal thymic tissue, as well as the peri-thymic fat in both the

neck and the mediastinum[3,4]. As such, surgical approach should enable the greatest possible resection for ectopic thymic tissue without recurrent laryngeal, vagus and phrenic nerve damage, unless these are invaded by the tumor[3]. The thymectomy in myasthenic patients without a thymoma is a discussion beyond the purpose of this work.

Four patients (22%) in our sample had collateral damage of the phrenic nerve, as depicted by unilateral diaphragm elevation on chest-CT after treatment. This represents a higher rate when compared with the 2% rate described in the literature3. This damage occurred in patients at different stages of the tumoral disease, which may suggest that this complication is independent of thymoma stage. One of them, in fact, had a surgical border next to the phrenic nerve, described in the anatomy pathology report. This treatment collateral effect could contribute to ventilatory abnormalities and thus can be misunderstood with MG progression, as these patients may present with dyspnea.

Different staging classifications are used for thymoma. The most widely used is Masaoka-Koga, which is based on histopathological and perioperative findings[8]. As noted in the literature, Masaoka's staging has proven to be an independent prognostic factor[14, 15].

Histological type B2 of the WHO classification system was the most frequently observed in this series of patients, which is consistent with other studies[7]. Histological type poorly correlates with clinical outcome[16].

To minimize the heterogeneity of our sample and considering that most of the patients had at least a three-year follow-up, except for two, we decided to classify the oncological disease evolution within that time interval. And, in fact, our 3-year survival rate was 81,2% and the median time of death since the thymectomy (in surgical patients) or biopsy (in non-surgical patients) was 1,3 years. The median time until recurrence / progression in the rest of the patients was 3 years.

In our sample, thymectomy clearly improved the oncological outcome with low recurrence / progression rate (16,6%) and low mortality (8,3%), when in comparison with the oncological progression (75%) of the non-surgical patients, and their death rate (50%).

Moreover, in our sample, resection margins were R0 in seven patients out of thirteen (53,8%), which means "clean margins", with no cancer cells seen microscopically at surgical specimen limits, and it may explain the good results with few recurrences observed, since only one R0 patient had recurrence. This is concordant with the literature17 and emphasizes why this must be a surgical goal.

Preoperative intravenous immunoglobulin (or plasmapheresis) should be performed in order to remove circulating pathological antibodies, and thus prevent clinical worsening after thymectomy[18]. In our sample, 25% of the patients (n=1) who did not receive preoperative intravenous immunoglobulin showed a postoperative myasthenic crisis. On the other hand, latest evidence has been suggesting that intravenous immunoglobulin is unnecessary in well-controlled myasthenia gravis patients[19].

Finally, we would like to share that it is still not clear if and how the presence of MG impacts the thymoma's progression and overall-survival. Recent investigations show that MG is not a prognostic factor in the thymoma treatment[20, 21].

This study shows some limitations, mainly due to the small size of our sample, but also because of its retrospective design. Additionally, and once more, we consider that the post-thymectomy follow-up time was limited in some of our most recent patients.

CONCLUSION

We believe that our sample helped us to become aware of important aspects concerning therapeutic orientation of these patients, such as the clinical impact of thymectomy in the course of MGAT and the prognostic value of the surgical resection margins. Finally, we would like to highlight that management of MG patients is only possible with a multidisciplinary approach and a close cooperation between Neurology, Oncology and Thoracic Surgery departments.

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