ORIGINAL ARTICLE

THE IMPACT OF THYMECTOMY IN THYMOMATOUS AND NONTHYMOMATOUS MYASTHENIA GRAVIS – THE EXPERIENCE OF A TERTIARY CENTER

Sara A. Cunha[1*], Pedro Faustino[2*], André Jorge[2], Luís L. Graça[1], Luciano Almendra[2], Anabela Matos[2], Luís Negrão[2], Rita Pancas[1]

[1] Thoracic surgery unit, Cardiothoracic Surgery, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[2] Neurology department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

* These authors contributed equally to the work

Abstract

Introduction: *Thymectomy remains a mainstay of treatment in Thymomatous (T) and Nonthymomatous (nT) Myasthenia Gravis (MG), with improved clinical outcomes and reduced need for medical treatment, however, there is little research regarding long-term follow-up.*

We aim to assess the impact of surgery on the long-term outcome of patients with MG at our center.

Methods: *Retrospective analyses of MG patients submitted to thymectomy between 2007 and 2017 at the thoracic surgery department of CHUC. Clinical assessment was performed according to the MG Foundation of America (MGFA) Clinical Classification (cMGFA). The follow-up was categorized according to the MGFA Post-intervention Status (MGFA-PIS) and cMGFA. Statistical analysis was performed with SPSS, to a significance level of 5%.*

Results: *Thirty-seven patients underwent extended thymectomy and 67.6% were female. Median age at diagnosis was 46.68±19.2 years. Most patients (83.8%) had anti-acetylcholine receptor antibodies and 81.1% had generalized forms of MG. Many patients (67.6%) had surgery less than 12 months after the clinical diagnosis. TMG was present in 19 (51.4%) patients. Compared to nTMG, these patients were older (54.06±17.9 vs 40.17±19.4 years) and most were men (52.9% vs 16.7%). We obtained a good outcome in most patients in the first (81.1%), second (86.1%), and fifth (84.8%) year of follow-up. There was a shift towards better prognosis categories in the good outcome group: 9.1% CSR, 3.0% PR, and 66,7% MM in the fifth year. Preoperative medical treatment did not influence the long-term follow-up outcome. A shorter time to surgery (< 12 months) correlated with better outcomes at year 5 (p=0.016).*

Conclusion: *Thymectomy led to a sustained clinical improvement in our cohort, allowing for a reduced need for medication. A shorter time to surgery seems to have a positive influence on long-term prognosis. We expect that an extended follow-up would improve our results.*

Keywords: *Myasthenia Gravis; Thymectomy; Thymoma; Nonthymomatous Myasthenia Gravis.*

INTRODUCTION

Myasthenia Gravis (MG) is an acquired autoimmune disease caused by autoantibodies against (ab+) components of the postsynaptic neuromuscular junction, leading to ocular or generalized muscle weakness. Most patients have ab+ against acetylcholine receptor (AChR);[1] however, other antibodies are now recognized to also cause MG, including muscle-specific tyrosine kinase (MuSK) and low-density lipoprotein receptor related protein 4 (Lrp4).[2]

It is long acknowledged that there is a relationship between the thymus and MG, however the mechanism is not fully understood. MG patients can present with a diverse thymic histology, being the most common thymic hyperplasia (80%). Thymoma is present in 10-15% patients with MG.[1,3]

In 1939 Blalock[4] first reported remission of generalized MG after thymic resection. Subsequently,

others reported encouraging results with thymectomy.[5,6] Nowadays, novel therapeutic advances have included the use of anticholinesterase drugs, corticosteroids and other immunosuppressive medications, however, thymectomy still plays a major role in the treatment strategy for MG.[1,7,8]

Once thymoma is suspected, thymectomy is indicated.[1,9] Regarding the nonthymomatous MG, the results of the Thymectomy Trial in Nonthymomatous MG (nTMG) Patients Receiving Prednisone (MGTX)7 demonstrated a significantly improved clinical outcome in patients submitted to thymectomy plus prednisone compared to prednisone alone.

Nevertheless, there is still some debate regarding factors that influence the response to thymectomy.[10,11]

This report will review the experience of our center regarding patients with MG consecutively treated with extended transsternal thymectomy and their long-term follow-up.

METHODS

Patients and Methods

Retrospective analysis of MG patients submitted to thymectomy between 2007 and 2017 at the thoracic surgery department of Centro Hospitalar e Universitário de Coimbra (CHUC). A total of 50 patients had a preoperative diagnosis of MG and underwent surgery. We excluded 9 patients that were misdiagnosed as MG, and 4 were later lost to follow-up, resulting in a total of 37 patients that we included in our analysis.

Neurologic Assessment

Diagnosis of MG was based on clinical history and neurological examination, electrophysiologic study with repetitive nerve and serum antibody determination (ab+ AChR or ab+ MusK). Seronegative patients all had electrophysiologic studies with decremental responses compatible with the diagnosis of MG.

The patients' preoperative clinical status was classified according to the MG Foundation of America (MGFA) clinical classification (cMGFA8). The follow-up was categorized according to the MGFA Post-intervention Status (MGFA-PIS8) and the cMGFA, and both classifications were assessed on year 1, 2 and 5 after the intervention. We defined "Good Outcome" as categories Complete Stable Remission (CSR), Pharmacological Remission (PR), Minimal Manifestations (MM) and Improved (I) and "Bad Outcome" as categories Unchanged (U), Worse (w), Exacerbation (E) or Death of MG (D).

Surgical Assessment and Technique

All patients had a preoperative chest computed tomography (CT) scan.

All the patients underwent extended transsternal thymectomy (T-3b8). This surgery was performed under general anesthesia using a single-lumen endotracheal tube intubation. Patients were set in supine position and the approach was a median sternotomy. The thymic tissue was removed together with the mediastinal fat in between the phrenic nerves, from thyroid gland to diaphragm.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and standard deviation (SD) or median and interquartile range (IQR), depending on the results of the normality test (Shapiro-Wilk test). For categorical variables, Fisher's exact test or the chi-square test was used, as appropriate, whereas for continuous variables with Student's t-test or Mann-Whitney test was used, depending on parametric distribution. Statistical analysis was performed using SPSS software version 25.0 (IBM Corp, 2017).

RESULTS

Table 1 summarizes the demographic and clinical characteristics of our population. A total of 37 patients underwent extended transsternal thymectomy, 67.6% were women, with a mean age of 46.68±19.2 years. Antibodies for AChR were positive in 83.8% and 81.1% had generalized forms of MG. Most patients (67.6%) underwent surgery in less than 12 months after diagnosis. All patients reached good control of myasthenic symptoms before surgery, having received preoperative optimization with plasmapheresis in 31 (83.8%) patients, intravenous immunoglobulin (IVIg) in 3 (8.1%), combination of IVIg and plasmapheresis in 2 (5.4%) and 1 (2.7%) patient had no treatment. No intraoperative adverse events occurred in this series. The median hospital stay was 5 days (range 3 to 26). Postoperative complications were registered in 16.2% (6 patients): bleeding requiring surgical revision (2 patients, 5.4%), myasthenic crisis with the need for re-intubation (3 patients, 8.1%) and phrenic paralysis (1 patient, 2.7%). No 30-day mortality was reported.

The most frequent histologic result was thymic hyperplasia in 48.6%, followed by thymoma in 45.9% and thymic carcinoma in 5.4%. In the thymoma group, most patients had localized disease (Masaoka stage I and IIA, 11 patients, 61.1%; TNM I, 11 patients, 61.1%).

We compared nonthymomatous versus thymomatous patients, excluding the 2 patients with thymic carcinoma. Compared with nonthymomatous MG, patients with thymoma were older (54.06±17.9 vs 40.17±19.4 years; p=0.029) and most were men (52.9% versus 16.7%; p=0.024). They also had worse preoperative clinical status (p=0.016). Thymoma patients had a tendency towards worse clinical status on follow-up at years 1, 2 and 5, but without significant difference as evaluated by the MGFA-PIS (p=0.157, p=0.294, p=0.281, respectively). Time to surgery was similarly brief in both thymomatous and nonthymomatous MG patients (0.41±0.62 vs 0.44±0.7 months; p=0.42). Detailed comparative description is shown in Table 2.

Table 1 **Baseline characteristics of study population**

Variables	Values
Mean age, years	46.68 ±19.2, 17-85 a
Female	25 (67.6)
Male	12 (32.4)
Antibodies	
Anti-AChR	31 (83.8)
Anti-MusK	1 (2.7)
Seronegative	5 (13.5)
Pre-operative cMGFAb	
I	7 (18.9)
IIa/IIb	13 (35.1) / 10(27.0)
IIIa/IIIb	2 (5.4) / 2 (5.4)
Iva /IVb	0 (0) / 3 (8.1)
Preoperative Medical Therapy	
IA	13 (35.1)
IA plus steroids	21 (56.8)
Regular Plasma Exchange or IVIg	3 (8.1)
Preoperative Optimization	
Plasma Exchange	31 (83.8)
IV Ig	3 (8.1)
No treatment	1 (2.7)
Time from diagnosis to surgery	
< 12 months	25 (67.6)
12 – 24 months	9 (24.3)
> 24 months	3 (8.1)
Mean Hospital Stay, days	5.0±4.0, 3-26a
Histology	
Thymic Hyperplasia	18 (48.6)
Thymoma	17 (45.9)
Thymic Carcinoma	2 (5.4)
Masaoka stage	
I	8 (44.4)
IIA	3 (16.7)
III	4 (22.2)
IVA	3 (16.7)
TNM	
I	11 (61.1)
IIIA	2 (11.1)
IIIB	1 (5.6)
IVA	4 (22.2)

Values are n (%) except age and hospital stay.
a(mean±SD, min-max).
bcMGFA: clinical classification developed by Myasthenia Gravis Foundation of America (MGFA). Patients with exclusive ocular weakness are considered class I; mild to severe generalized weakness are considered Class II to IV, respectively; fulminant generalized weakness with need of invasive mechanical ventilation are classified as class V.8
IA: Inhibitors of Acetylcholinesterase. IVIg

Regarding overall functional outcomes, we obtained a good outcome in most patients in the first (81.1%), second (86.1%), and fifth (84.8%) year of follow-up. Table 3 describes possible prognostic variables and their distribution in the two groups. A shorter time to surgery (< 12 months) correlated with better outcomes at year 5 (p=0.016). Age, gender, positivity for AChR antibodies (versus seronegative patients), preoperative clinical status and medical treatment, and thymic histology did not influence the long-term outcome.

In a sub-analysis, most patients presented cMGFA status ≤ IIIa at the time of surgery (86.5%) and there were no differences when comparing the long-term outcomes between these patients and patients with more severe preoperative status at years 1, 2 and 5 (p=0.89, 0.467, 0.390, respectively).

We also performed a sub-analysis of patients with ocular MG (cMGFA I), shown in Table 4. We operated on 7 patients, with most of them having a good outcome at year 1, 2 and 5 (6 patients, 85.7%). Only one patient developed a generalized form. The overall prognosis was worse in the patients with thymoma (3 patients, 42.9%) with one patient dying 5 years after the procedure, with a myasthenic crisis in the context of bilateral pneumonia.

From the first to the fifth year of follow-up, there was a shift towards better prognosis categories in the good outcome group: 9.1% CSR, 3.0% PR, and 66,7% MM in the fifth year, as shown in figure 1 and table 5. Only 1 patient died from myasthenic crisis triggered by bilateral pneumonia, 5 years after surgery. Additionally, 4 patients died from unrelated causes.

DISCUSSION

The exact connection between the thymus and MG is not well understood, nevertheless, it is known that MG is caused by IgG antibodies against the AChR complex, and the thymic pathology contributes to errors in the mechanisms of self-tolerance.[12] Current guidelines and consensus recommend thymectomy in anti-AChR+ generalized MG.[1,13–15]. As expected in a thymectomy setting, our cohort has a predominance of generalized forms of MG, with ab directed against AChR. Only one patient present with ab against MuSK, and according to the current literature, there is no advantage and even poor post-interventional prognosis in patients with MG associated with these ab.[1,13,16,17]

In our cohort there is a younger female predominance, which is in line with the main histological diagnosis of thymic hyperplasia and is concordant with literature.[12]

Thymectomy in patients with ocular MG (cMGFA I) remains controversial, considering that limited symptoms may not justify an invasive procedure. However, diplopia and ptosis might impair quality of life, and some studies[11,18] shown that in selected patients there might be a benefit

Table 2 **Patients characteristics based on histology**

	MG + Nonthymomatous	MG + Thymomatous	p-value
n	18	17	
Age (years)	40.17±19.4	54.06±17.9	0.029
Gender (male)	3 (16.7)	9 (52.9)	0.024
Preoperative cMGFAa			
I	4 (22.2)	3 (17.6)	0.016
IIa	4 (22.2)	8(47.1)	
IIb	8 (44.4)	1 (5.9)	
IIIa	0 (0)	2 (11.8)	
IIIb	2 (11.1)	0 (0)	
IVa	0 (0.0)	0 (0.0)	
IVb	0 (0)	3 (17.6)	
Preoperative treatment			
IA	6 (33.3)	7 (37.1)	0.359
IA plus steroids	10 (55.6)	10 (58.8)	
Regular Plasma Exchange or IVIg	2 (11.1)	0 (0)	
Preoperative Optimization Therapy			
No treatment	1 (5.6)	0 (0)	0.511
Plasma Exchange	15 (83.3)	15 (88.2)	
IVIg	1 (5.6)	2 (11.8)	
Plasma Exchange + IVIg	1 (5.6)	0 (0)	

Values are presented as n (%).
acMGFA: clinical classification developed by Myasthenia Gravis Foundation of America (MGFA).8

in performing thymectomy, specially nowadays, with the development of minimal invasive techniques[19]. In our subgroup analysis, most patients (85.7%) had a good outcome at year 1, 2 and 5, with patients with MG associated with thymoma (42.9%) presenting with worse follow-up results

The impact of thymectomy in the treatment of MG has been debated for long given the lack of prospective studies.[20] The randomized trial of thymectomy in MG (MGTX7) proved a benefit in patients with nonthymomatous MG submitted to surgery plus prednisone compared to prednisone alone, with better clinical outcomes: reduction in mean quantitative MG scores and prednisone doses, with more patients reaching the MM status (MGFA-PIS8). As for thymomatous MG, thymectomy is usually recommended, regardless of the MG severity.[1,13] Regarding histology, in our series we have thymic hyperplasia in 48.6% and thymoma in 45.9%. Some studies indicate that thymomathous MG is associated with greater severity and poorer outcome.[10,21] In fact, in our series, preoperative clinical status (cMGFA) is worse in the thymoma group. On follow-up, these patients have a tendency towards worse clinical status (cMGFA), but there is no significant difference as evaluated by MGFA-PIS (table 2), with both groups benefiting from the intervention. The effects of thymectomy may have a long delay, so the surgery should be performed as an elective procedure, when the patient is stable and capable of undergoing an intervention that can limit the respiratory function.[1,13] At our center, most patients underwent preoperative optimization with plasma exchange. Plasma exchange can be a short-term treatment, especially in severe cases and in preparation for surgery.[1,13]

Regarding surgery, there are several types of thymectomy classified according to extent of surgery

Table 3 **Predictive factors of response after thymectomy at year 1, 2 and 5**

	Year 1		p-value	Year 2		p-value	Year 5		p-value
	Good Result	Bad Result		Good Result	Bad Result		Good Result	Bad Result	
n (%)	30(80.1)	7(18.9)		31(86.1)	5(13.9)		28(84.8)	5(15.2)	
Age (years)	46.2(3.5)	36.0(6.4)	0.458	46.8(3.1)	19.7(1.5)	0.594	45.7(3.4)	36.4(8.8)	0.268
Gender (male)	10(33.3)	2(28.6)	0.809	10(32.3)	1(20.0)	0.581	8(28.6)	2(40.0)	0.609
Serum Antibodies									
Anti-AChR	24(80.0)	7(100)	0.434	25(80.6)	5(100)	0.560	22(78.6)	5(100)	0.520
Anti- MuSK	1(3.3)	0(0.0)		1(3.2)	0(0.0)		1(3.6)	0(0.0)	
Seronegative	5(16.7)	0(0.0)		5(16.1)	0(0.0)		5(17.9)	0(0.0)	
Preoperative cMGFAa									
I	6(20.0)	1(14.3)	0.800	7(22.6)	0(0.0)	0.537	6(21.4)	1(20.0)	0.593
IIa	11(36.7)	2(28.6)		9(29.0)	3(60.0)		10(35.7)	1(20.0)	
IIb	7(23.3)	3(42.9)		9(29)	1(20.0)		6(21.4)	3(60.0)	
IIIa	2(6.7)	0(0.0)		2(6.5)	0(0.0)		2(7.1)	0(0.0)	
IIIb	2(6.7)	0(0.0)		2(6.5)	0(0.0)		2(7.1)	0(0.0)	
IVa	0(0.0)	0(0.0)		0(0.0)	0(0.0)		0(0.0)	0(0.0)	
IVb	2(6.7)	1(14.3)		2(6.5)	1(20.0)		2(7.1)	0(0.0)	
Preoperative treatment									
IA	11(36.7)	2(28.6)	0.088	12(38.7)	1(20)	0.5	13(46.4)	0(0)	0.086
IA plus steroids	19(60)	3(42.9)		17(54.8)	3(60)		14(50)	4(80)	
Regular Plasma Exchange or IVIg	1(3.3)	2(28.6)		2(6.5)	1(20)		1(3.6)	1(20)	
Preoperative Optimization Therapy									
No treatment	0(0)	1(14.3)		1(3.2)	0(0)	0.696	0(0)	1(20)	0.09
Plasma Exchange	26(86.7)	5(71.4)		26(83.9)	4(80)		23(82.1)	4(80)	
IVIg	2(6.7)	1(14.3)	0.15	2(6.5)	1(20)		3(10.7)	0(0)	
Plasma Exchange + IVIg	2(6.7)	0(0)		2(6.5)	0(0)		2(7.1)	0(0)	
Histology									
Thymic Hyperplasia	16(53.3)	2(28.6)		16(51.6)	2(40)	0.686	16(57.1)	2(40)	0.631
Thymoma	12(40)	5(71.4)	0.4301	13(41.9)	3(60)		11(39.3)	3(60)	
Thymic Carcinoma	2(6.7)	0(0)		2(6.5)	0(0)		1(3.6)	0(0)	
Time to surgery after diagnosis									
< 12 months	22(73.3)	3(42.9)		20(64.5)	4(80.0)	0.706	20(71.4)	1(20.0)	0.016
12 – 24 months	6(20.0)	3(42.9)	0.300	8(25.8)	1(20.0)		7(25.0)	2(40.0)	
> 24 months	2(6.7)	1(14.3)		3(9.7)	0(0.0)		1(3.6)	2(40.0)	

Values are n (%)
acMGFA: clinical classification developed by Myasthenia Gravis Foundation of America (MGFA).8
IA: Inhibitors of Acetylcholinesterase. IVIg: Intravenous Immunoglobulin

Table 4 **Ocular MG follow-up sub analysis**

Patients		Year 1		Year 1		Year 5	
	Histology	cMGFAa	MGFA-PISb	cMGFA	MGFA-PIS	cMGFA	MGFA-PIS
1	Thymoma	0	W	0	I	0	MM
2	Thymoma	I	MM	0	MM	V	D of MG
3	Thymic Hyperplasia	0	MM	0	MM	0	MM
4	Thymic Hyperplasia	0	MM	0	MM	0	MM
5	Thymic Hyperplasia	0	MM	0	MM	0	MM
6	Thymic Hyperplasia	0	MM	0	MM	0	MM
7	Thymoma	I	MM	I	MM	I	MM

acMGFA: clinical classification developed by Myasthenia Gravis Foundation of America (MGFA).[8]
bMGFA-PIS: MGFA Post-intervention Status.[8]

Table 5 **MGFA-PIS assessment at year 1, 2 and 5.**

	Year 1	Year 2	Year 5
Complete Stable Remission (CSR)	0 (0)	2 (5.6)	3 (9.1)
Pharmacologic Remission (PR)	0 (0)	0 (0)	1 (3.0)
Minimal Manifestations (MM)	24 (64.9)	23 (62.2)	22 (66.7)
Improved (I)	6 (16.2)	6 (16.2)	2 (6.1)
Unchanged (U)	1 (2.7)	1 (2.8)	0 (0)
Worse (W)	5 (13.5)	4 (11.1)	5 (12.1)
Exacerbation (E)	1 (2.7)	0 (0)	0 (0)
Died of MG (D)	0 (0)	0 (0)	1 (3.0)

n (%)
MGFA-PIS: MGFA Post-intervention Status.[8]

and method of approach.[22] The extended transsternal thymectomy (T3-b8) was the approach of choice at our center at the time to which this study concerns and was associated with no post-operatory mortality and low rate of complications.

A patient with complete stable remission (CSR) is defined by MGFA as a patient with no symptoms or signs of MG (except ptosis) for at least one year and has received no therapy for MG during that time.[8] In our cohort, there is no CSR at year one, however, at year five there is 9.1%. Some series present higher rates of CSR after surgery and this tends to be higher in series with longer follow-up.[5,7] We propose that a longer follow-up would in fact improve our CSR rates.

Age and gender as prognostic factors show different associations among studies[10,21,23], however, in our work neither shows prognostic impact. Positivity for AChR ab (versus seronegative patients) does not seem to be a prognostic factor, but it is important to note the disproportionate comparison between groups (31 versus 5 patients). The same regards the comparison between lower and higher cMGFA preoperative status - this being an

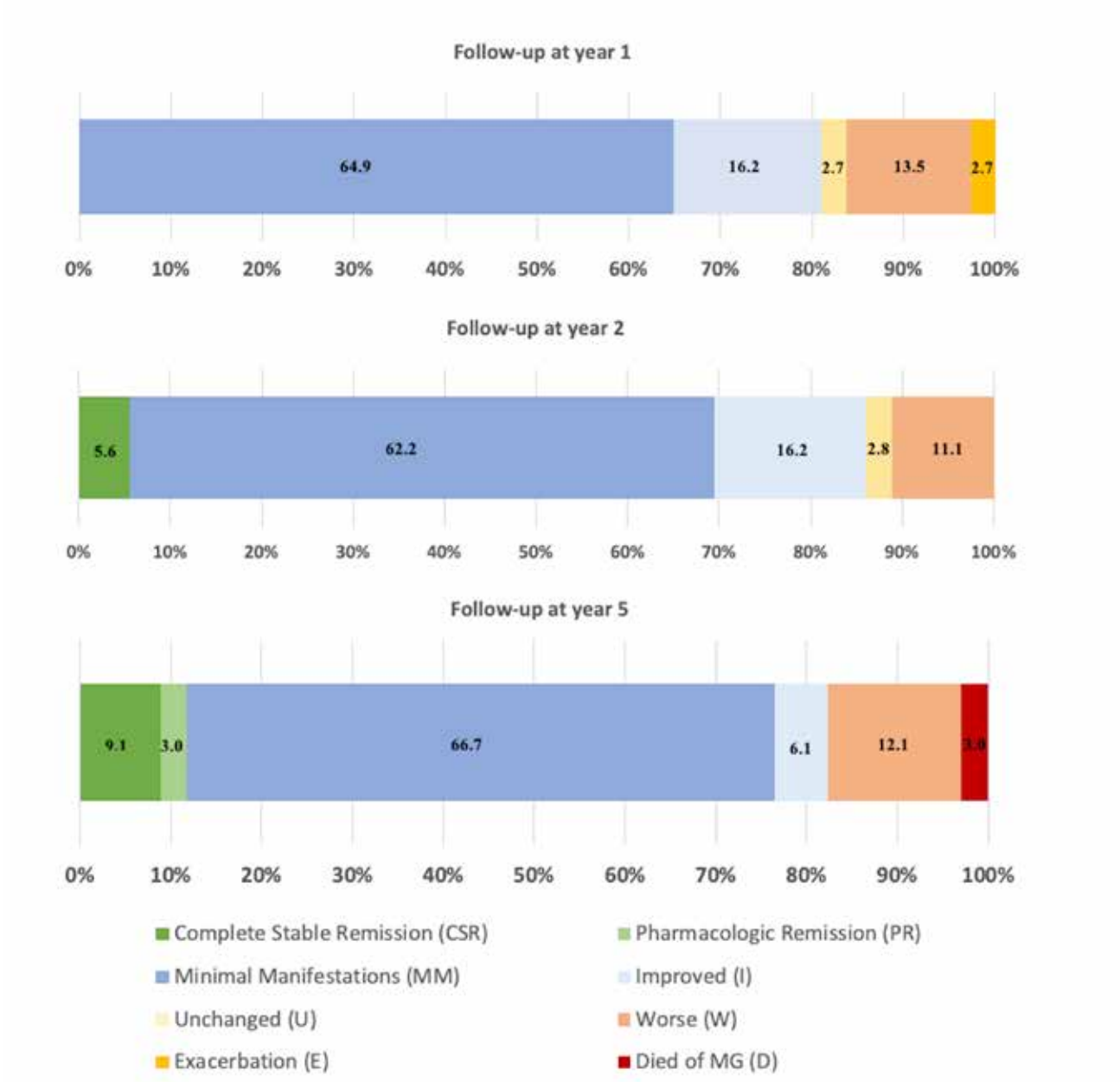

Figure 1 *Follow-up distribution according to MGFA-PIS8 at year 1, 2 and 5. At year 5 after thymectomy, 9.1% of the patients were in CSR and 84.8% had a good outcome.*

obvious selection bias, where most patients admitted for surgery are preferred to be in a stable phase of their MG.

Finally, our series is in line with the hypothesis that the duration of the disease is an important prognostic factor after surgery[5]. Our patients submitted to surgery less than twelve months after diagnosis presented with better outcomes at year 5, but interestingly not at year 1 and 2. This also underlines the delayed effect of thymectomy on MG control and the importance of a long-term follow-up of these patients.

CONCLUSION

In conclusion, thymectomy is an efficient treatment for MG and it is recommended as part of a multimodal therapy for generalized MG associated with ab AChR+, allowing for reduction of immunosuppressive and immunomodulatory drugs and associated with high rates of MM and CSR, especially after a long-term follow-up.

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