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CLINICAL SERIE

Surgical results of video-assisted thoracoscopic thymectomy for treatment of Juvenile Myasthenia Gravis

Resultados quirúrgicos de la timectomía por videotoracoscopía en el tratamiento de la Miastenia Gravis Juvenil

Josefina Sáez[a], María Jesús Irarrázaval[a], Cristina Vidal[a], Felipe Peralta[a], Raúl G. Escobar[b], Daniela Ávila[b], Mario Concha[c], Fernando Vuletin[a], Juan Carlos Pattillo[a]

[a]Sección de Cirugía Pediátrica, División de Cirugía, Escuela de Medicina, Facultad de Medicina, Pontificia Universidad Católica de Chile. Santiago, Chile.
[b]Unidad de Neurología Pediátrica, División de Pediatría, Escuela de Medicina, Facultad de Medicina, Pontificia Universidad Católica de Chile. Santiago, Chile.
[c]División de Anestesiología, Escuela de Medicina, Facultad de Medicina, Pontificia Universidad Católica de Chile. Santiago, Chile.

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What do we know about the subject matter of this study?

Myasthenia gravis (MG) is an autoimmune disease characterized by the presence of antibodies against neuromuscular junction elements in the postsynaptic membrane. Its treatment is mainly pharmacological, but thymectomy has shown improvement in remission rates.

What does this study contribute to what is already known?

This study describes a national experience of patients with juvenile myasthenia gravis who underwent thymectomy by video-assisted thoracoscopic surgery, with good surgical results and improvement of symptoms.

Abstract

Juvenile myasthenia gravis (JMG) is an autoimmune disease affecting the neuromuscular junction that appears before 19 years of age with varying degrees of weakness of different muscle groups. The main treatment is pharmacological, but thymectomy has also demonstrated to improve remission rates. **Objective:** To describe the clinical characteristics and postoperative course of pediatric patients with JMG who underwent video-assisted thoracoscopic (VATS) thymectomy. **Clinical Serie:** Six patients who underwent VATS thymectomy between March 2011 and June 2019. The age range at diagnosis was between 2 and 14 years and the average age at surgery was 7 years. All patients were under treatment with pyridostigmine bromide associated with immunosuppression with corticosteroids before surgery. The interval between diagnosis and thymectomy was 21.5 months on average. VATS was performed by left approach, and there was no perioperative morbidity or mortality. The average

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Correspondence:
Dr. Juan Carlos Pattillo
jpattillo@ucchristus.cl

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hospital stay was 2 days. Three patients remain with no symptoms and without corticotherapy. Two patients were on corticosteroids, but in smaller doses than previous to surgery. One patient presented a crisis requiring hospitalization and ventilatory support during follow-up. **Conclusion:** VATS thymectomy is part of the treatment for JMG. In this series, it appears as a safe approach and its results were favorable.

Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by the presence of antibodies against neuromuscular junction elements in the postsynaptic membrane. Patients experience fluctuating weakness of different muscle groups and symptoms are exacerbated by muscular activity and stress[1].

In the pediatric age group, this disorder can appear in two forms, transient neonatal MG, defined by the presence of maternal antibodies that are passively transferred through the placenta, and juvenile myasthenia gravis (JMG)[2]. The latter form of presentation appears before the age of 19 years, its incidence is estimated between 1 to 5 cases per million inhabitants per year[3], and has been described to be more frequent in the Asian population[4]. Ocular myasthenia exclusively affects the extraocular musculature and, if the disease affects any other muscle group, it is classified as generalized myasthenia[5].

Its diagnosis is based on clinical presentation and is supported by the presence of an abnormal decrease in the repeated nerve stimulation test, abnormal neuromuscular jitter in the single-fiber EMG test, positive tensilon test, and the presence of specific antibodies[6]. Medical treatment is the mainstay of therapy in JMG which includes pyridostigmine bromide as monotherapy or in association with immunosuppression with glucocorticoids, azathioprine, immunoglobulin, and plasmapheresis, among others[7].

Although its pathogenesis is not entirely clear, it is recognized that the thymus plays a central role in the development of the disease where occurs the maturation of T cells. Thymic hyperplasia has been reported in biopsies in patients who had their thymus removed[7]. Since the beginning of the 20th century, the role of thymectomy in MG has been investigated[8], recognizing that it produces symptoms improvement, reduction in drug requirements, and even remission of the disease[7]. Currently, thymectomy is accepted as a treatment for MG in adulthood[9,10].

The decision about the timing of surgery is based on a subjective balance between the benefits of thymectomy and the risks and sequelae of thoracic surgery, according to the type of approach. In recent years, these risks have been reduced by the development of minimally invasive surgical techniques, such as video-assisted thoracoscopic surgery (VATS), which allows a shorter recovery time, the absence of cosmetic sequelae, and a lower risk of complications. Although the available evidence for the pediatric population is scarce and mainly based on retrospective studies, the potential benefits associated with VATS thymectomy make it an attractive alternative in the treatment of these patients[11]. In addition, comparative studies show that VATS thymectomy is a reasonable option to be performed at different stages of the disease during the pediatric age[12].

In Chile, a previous experience has been reported with favorable evolution[13,14]. The improvement of thoracoscopy and imaging techniques suggests that VATS could currently be associated with a better clinical evolution, with less morbidity than previously reported.

The objective of this work is to describe the clinical characteristics and evolution of six pediatric patients with JMG undergoing VATS thymectomy.

Patients and Method

Six pediatric patients with a diagnosis of juvenile MG underwent VATS thymectomy between March 2011 and June 2019. Table 1 shows the clinical data of the series.

The diagnosis of JMG was confirmed in all patients by a positive tensilon test or a compatible peripheral neurophysiological study with repeated nerve stimulation test and by the presence of anti-acetylcholine receptor antibodies detected by radioisotope technique. All patients were monitored by a pediatric neurologist and used pyridostigmine bromide in association with glucocorticoids as pharmacological treatment. Two patients required hospitalization, but without respiratory or nutritional support. One of them required administration of IV immunoglobulin.

At the time of preoperative evaluation, three patients had secondary Cushing's syndrome and the remaining three had persistent motor symptoms despite the increasing dose of corticosteroids. The interval between diagnosis and surgical intervention was 21.5 months (6 - 57 months). Tables 1 and 2 show the severity of the disease, classified according to Osserman

and Genkins criteria[15] at the time of surgery. All patients were evaluated with a CT scan or MRI, ruling out the presence of mediastinal masses or unfavorable laterality for surgery (figure 1).

The thymectomies were performed by left VATS under general anesthesia and orotracheal intubation, with 30º head-end elevation and extended left arm. Access was through the 4th intercostal space, in the mid-axillary line with blunt dissection. CO2 insufflation up to 4 mmHg with flows between 1 and 5 liters per minute was used. Two auxiliary trocars were positioned on both sides of the optics. After having identified the phrenic nerve and the internal mammary artery, the dissection of the thymus was performed by opening the parietal pleura. Mono- and bipolar coagulation and advanced hemostats were used as needed. We were especially careful to complete the dissection of the thymus towards the right side, after identifying the contralateral phrenic nerve, and completing the dissection towards the neck, ensuring complete removal of the gland.

No perioperative morbidity was recorded. Specifically, there was no significant bleeding, and no transfusions were indicated. The average time of surgery was 160 minutes (127-210 minutes). During their immediate postoperative period, the patients were transferred to the Critical Patient Unit or Intermediate Care Unit, mainly for monitoring. An analgesia scheme based on acetaminophen by schedule and rescue non-steroidal anti-inflammatory drugs was indicated, with good response in all patients. Pleurostomy was used in the first 4 patients, which was removed on average on the second postoperative day, with no air leak or significant effusion. By surgeon's choice, the last two patients did not require pleural tube installation in the operating room nor the postoperative period. The average hospital stay was 2 days (1 - 3 days). No mortality was recorded in this series.

The anatomic pathology report showed thymic hyperplasia in four cases. The fifth patient had a biopsy which showed thymolipoma and the last patient presented cystic dilatations and calcifications in the thymic parenchyma.

The median follow-up was 29.6 months. To date only the patient that presented thymolipoma has had a myasthenic crisis that required ventilatory support, immunoglobulin administration, plasmapheresis, and rituximab. Currently, three patients remain without corticotherapy. One patient achieved discontinuation of prednisone but had to restart it at half the dose he was using before surgery. The remaining patient failed to discontinue corticosteroids in the postoperative period, although he is currently using a 25% lower dose. Table 3 summarizes the data considering the use of drugs with anticholinesterase action and immunosuppression with corticosteroids or other drugs.

Table 1. Clinical characteristics of patients with Juvenile Myasthenia Gravis (JGM) who underwent thymectomy by video-assisted thoracoscopy.

Patient	Gender	Age at diagnosis	Age at surgical intervention	Weight at surgical intervention (kg)	Osserman's classification
1	M	2 y	2 y 8 m	14	IIA
2	M	13 y	13 y 6 m	68	IIB
3	F	2 y 9 m	4 y 10 m	21	IIA
4	M	3 y	7 y 9 m	23	IIA
5	F	14 y	15 y	65	IIB
6	F	2 y	2 y 11 m	15,4	IIA

M: male; F: female.

Table 2. Osserman Criteria for Myasthenia Gravis (ref 15)

I	Ocular	Only ocular involvement
IIA	Mild Generalized	Generalized muscle involvement without respiratory muscle involvement.
IIB	Moderate Generalized	Bulbar manifestations.
III	Acute fulminating	Rapid onset (within 6 months) of severe bulbar and skeletal muscles involvement with important weakness. Respiratory muscles are involved.
IV	Late severe	Progressive in severity for 2 or more years.

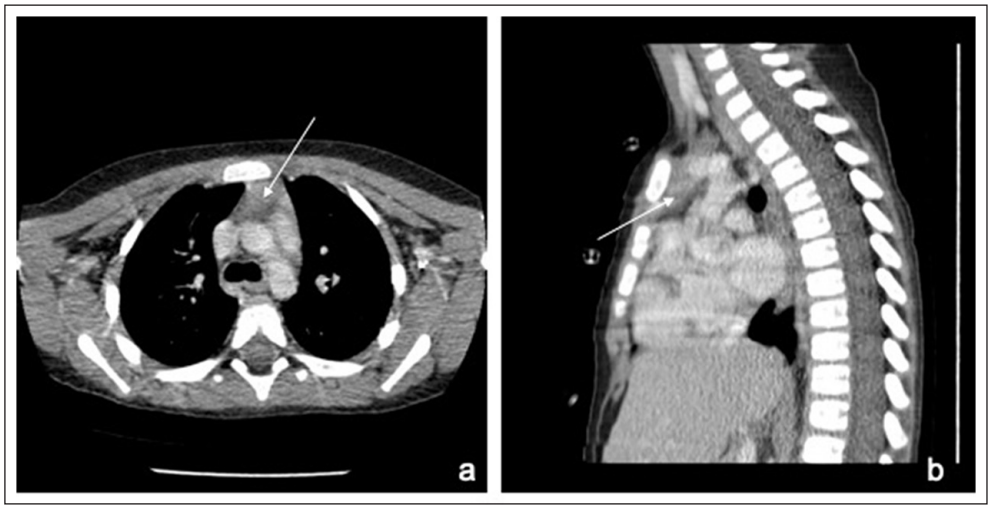

Figure 1. Chest computed tomography with contrast. The thymus is identified with an arrow in axial (a) and sagittal (b) view, of normal size for the age of this patient.

The cosmetic results of this technique were favorable since the three incisions no larger than one centimeter were performed under the armpit (figure 2).

Discussion

Thymectomy in MG was originally reserved for patients refractory to medical treatment or with progressive symptoms and generalized disease[18]. However, it is currently accepted in adult patients within the therapeutic options, without the need to meet the aforementioned criteria[10].

In 1970 was published the first paper that reported the effect of thymectomy for JMG. In 20 years, 14 pediatric patients refractory to medical treatment were managed with thymectomy,12 of them improved their symptoms, and 2 achieved complete remission of the disease[19]. Subsequently, other series have been published supporting thymectomy as an effective and safe complementary treatment in JMG, as it would reduce symptoms, frequency of crises and even eliminate the need for immunosuppressive treatment. A systematic review published in 2009, on 50 years of pediatric literature, identified 19 studies that included 479 patients, which reported 68% of symptomatic improvement after thymectomy, although follow-up times were not specified[20].

Wolfe et al. recently published the first randomized clinical trial comparing the use of corticosteroids versus corticosteroids plus thymectomy for the treatment of adult patients with MG. In the corticosteroid plus thymectomy group, the MG severity scale was lower compared with the corticosteroid group ($p < 0.001$) during the 36-month follow-up. They also demonstrated differences related to the dose of corticosteroids used, where the thymectomy group reduced by 16 mg on average the dose of prednisone taken throughout the study (95% CI, 7 to 25mg. $p < 0.001$). Other secondary outcomes that favoured the thymectomy group were fewer hospitalizations due to exacerbations (9% vs. 37%, $p < 0.001$), fewer participants with symptoms, fewer total symptoms, less discomfort associated with symptoms, and no differences in treatment complications in both groups[10]. It constitutes the strongest evidence to support thymus resection in MG patients.

Table 3. Postoperative clinical status according De Filippi Classification (ref 17)

Class	Description	
1	Complete remission, no medication.	
2	Asymptomatic, decreased medication.	3 patients
3	Improved, decreased symptoms or decreased medication.	2 patients
4	No change in symptoms or medication use.	
5	Worse of symptoms	1 patient (myasthenic crisis during follow up)

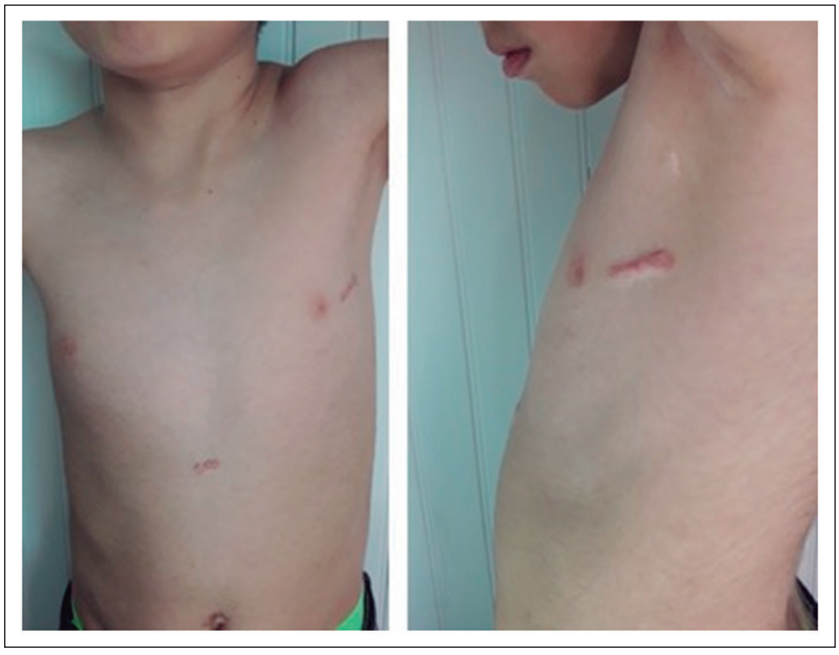

Figure 2. Frontal and lateral view of the scars, two years and five months after surgery.

Although there is consensus on the benefit of thymectomy, there is still no agreement on the ideal time to perform the surgery, whether to first exhaust medical treatment or to do it early in the course of the disease. An initial approach could propose to perform it before the year of onset of generalized symptoms, thus reducing the time of exposure to corticotherapy and its adverse effects and increasing the probability of remission[5]. Other authors propose waiting until the end of prepuberty to allow the thymus to fulfill its function in the development of the immune system[21]. In any case, it is necessary to mention that the expected improvement after thymectomy is not related to the age at surgery, since it is also determined by external factors such as social, infectious, physical, and emotional stressors[7].

The development of minimally invasive techniques such as VATS offers a safe treatment option, with low morbidity and without the cosmetic sequelae of a sternotomy[7]. Among the advantages offered by VATS are a surgery time equal to or less than that of thymectomy by sternotomy, lower rates of hemorrhage, hospital stay, and morbidity associated with the incision[7]. However, demonstrating the same effectiveness between thoracoscopic and open surgery is difficult with retrospective data, which compare different cohorts in the behavior of the disease, in the preoperative period, and do not standardize the selection of patients for surgery[12]. The available information places VATS thymectomy as not inferior in results to the open approach but raises questions about incomplete resections and lower remission rates[22]. Prospective studies in adults have shown superiority of robotic surgery when compared with VATS in patients with MG who underwent thymectomy[23], showing higher remission rates. However, there is still no evidence in pediatric patients and the availability of robotic surgery in our country is limited.

Our analyzed series includes only thoracoscopic surgery but shows good results in terms of surgical morbidity and mortality, effect on the disease motivating the intervention, and agrees with other available series[6-7,12,19-20].

The main weakness of this report is the retrospective design with data collection limited by the medical report in the registries. However, this publication contributes by adding a series of patients who underwent VATS thymectomy for JMG in our country, to other experiences presented by a national group of 35 children, where one of them had a lesion of the phrenic nerve that led to a diaphragmatic surgery[13,14].

In conclusion, in this series of patients with JMG, thymectomy by VATS was a safe technique and its functional results are at least comparable with thymectomy by median sternotomy, avoiding its cosmetic sequelae. In addition, we believe that the early performance of thymectomy would favor patients with generalized symptoms by offering a shorter exposure time to corticosteroids.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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References

1. Kim AG, Upah S, Brandsema J, et al. Thoracoscopic thymectomy for juvenile myasthenia gravis. Pediatr Surg Int. 2019;35(5):603-10.
2. Papazian, O. Transient Neonatal Myasthenia Gravis. J Child Neurol. 1992;7(2):135-41.
3. McGrogan A, Sneddon S, de Vries CS. The incidence of Myasthenia Gravis: A systematic literature review. Neuroepidemiology. 2010;34(3):171-83.
4. Zhang X, Yang M, Xu J, et al. Clinical and serological study of myasthenia gravis in HuBei Province, China. J Neurol Neurosurg Psychiatry. 2007;78(4):386-90.
5. Peragallo JH. Pediatric myasthenia gravis. Semin Pediatr Neurol. 2017;24(2):116-21.
6. Ionita CM, Acsadi G. Management of juvenile myasthenia gravis. Pediatr Neurol. 2013;48(2):95-104.
7. Christison-Lagay E, Dharia B, Vajsar J, Kim PC. Efficacy and safety of thoracoscopic thymectomy in the treatment of juvenile myasthenia gravis. Pediatr Surg Int. 2013;29(6):583-6.
8. Blalock A, Mason MF, Morgan H, et al. Myasthenia gravis and tumors of the thymic region. Ann Surg. 1939;110(4):554-61.
9. Li F, Li Z, Chen Y, et al. Thymectomy in ocular myasthenia gravis before generalization results in a higher remission rate. Eur J Cardiothorac Surg. 2020;57(3):478-87.
10. Wolfe G, Kaminski H, Aban I, et al. Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med. 2016;375(6):511-22.
11. Catalano M, Mullan C, Rich B, et al. Pediatric thymectomy: a study of national trends in demographics, short-term outcomes, and cost. Pediatr Surg Int. 2019;35(7):749-57.
12. Goldstein SD, Culbertson NT, Garrett D, et al. Thymectomy for myasthenia gravis in children: a comparison of open and thoracoscopic approaches. J Pediatr Surg. 2015;50(1):92-7.
13. Blanco A, Poblete M, Gómez N, et al. . Timectomía toracoscópica en miastenia gravis. Congreso chileno de cirugía pediátrica. Coyhaique, Chile. Rev Ped Elec. [en línea] 2006, Vol 3, N° 3.
14. González G, Blanco A, Kleinsteuber K, et al. Miastenia Gravis, tratamiento quirúrgico en la edad pediátrica. XII Congreso de Cirugía Pediátrica del Conosur de América. Asunción, Paraguay. 2017.
15. Drachman D, Adams R, Josifek L, et al. Functional Activities of Autoantibodies to Acetylcholine Receptors and the Clinical Severity of Myasthenia Gravis. N Engl J Med. 1982;307(13):769-75.
16. Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
17. DeFilippi V, Richman D, Ferguson M. Transcervical thymectomy for myasthenia gravis. The Annals of Thoracic Surgery. 1994;57(1):194-97.
18. Sonett JR, Magee MJ, Gorenstein L. Thymectomy and myasthenia gravis: A history of surgical passion and scientific excellence. J Thorac Cardiovasc Surg 2017;154(1):306-9.
19. Fonkalsrud EW, Herrmann C, Mulder DG. Thymectomy for myasthenia gravis in children. J Pediatr Surg. 1970;5:157-65.
20. Tracy MM, McRae W, Millichap JG. Graded response to thymectomy in children with myasthenia gravis. J Child Neurol. 2009;24:454-59.
21. Sanders D, Wolfe G, Benatar M, et al. International consensus guidance for management of myasthenia gravis. Neurology. 2016;87(4):419-25.
22. Ponseti J, Gamez J, Vilallonga R, et al. Influence of ectopic thymic tissue on clinical outcome following extended thymectomy in generalized seropositive non thymomatous myasthenia gravis. Eur J Cardiothorac Surg. 2008;34(5):1062-7.
23. Rückert J, Swierzy M, Ismail M. Comparison of robotic and nonrobotic thoracoscopic thymectomy: A cohort study. The Journal of Thoracic and Cardiovascular Surgery 2011;141(3):673-7.