Editorial

Thymectomy for non-thymomatous myasthenia gravis: the end of controversy, albeit fifty years late

Josep Gamez, José Maria Ponseti

Myasthenia Gravis Unit, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute, Autonomous University of Barcelona, Barcelona, Spain
Correspondence to: Josep Gamez, MD, PhD. Myasthenia Gravis Unit, Neurology Department, Vall d'Hebron University Hospital, Autonomous University of Barcelona, VHIR, Passeig Vall d'Hebron, 119, Barcelona, Spain. Email: josepgamez.bcn@gmail.com.
Comment on: Wolfe GI, Kaminski HJ, Aban IB, *et al*. Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med 2016;375:511-22.

Received: 10 November 2016; Accepted: 30 November 2016; Published: 21 January 2017.
doi: 10.21037/jxym.2017.01.02
View this article at: http://dx.doi.org/10.21037/jxym.2017.01.02

The recent publication of the first international, multicenter, prospective, singled-blinded, and randomized trial (MGTX trial) comparing extended transsternal thymectomy plus alternate-day prednisone with prednisone alone in generalized non-thymomatous myasthenia gravis (MG) provides an answer and ends a long-running debate on the role and effectiveness of thymectomy in the treatment of non-thymomatous MG patients (1). An initial reading of the results for a three-year period confirms that thymic resection is superior to medical treatment with prednisone alone in these patients. This trial has provided evidence that thymectomy still has an important role to play in the standard treatment of MG.

Thymectomy gained widespread acceptance as a modality of treatment in patients with MG after Blalock *et al.* reported their landmark series demonstrating relief from MG symptoms after removal of the thymus (2). The findings supported thymectomy as a treatment option in myasthenic patients, especially in those with milder forms of generalized MG (3-6). However the precise mechanism of action of thymectomy is unknown, although possible explanations include removal of the source of continued antigen stimulation, removal of acetylcholine receptor (AChR) antibody-secreting B cells and immunomodulation (7-15).

The effectiveness of thymectomy has been called into question over the last four decades, basically due to the absence of controlled randomized prospective studies, despite evidence that the condition of many patients improved and their reduced requirements of prednisone and pyridostigmine after surgery. In general, the benefits of thymectomy are delayed for months or years (10,16-24). According to life table analyses of remission rates comparing the results after six different types of resectional technique (T1-a or cervical basic, T-1b or extended cervical, T-2a or classic video-assisted thoracic surgery thymectomy-VATS, T-2b or video-assisted thoracoscopic extended thymectomy-VATET, T-3b or extended transsternal, and T-4 or combined transcervical-transsternal), between 3% and 24% of the thymectomized patients achieve remission in the first year after thymus resection. This variable success depends on the thymectomy technique used. Significantly, the highest remission rates are achieved in the fifth year after surgery, ranging between 25% and 55% of patients. Most experts believe that post-thymectomy evaluation at 5 years is a good starting point to evaluate remission rates and effectiveness after thymus resection. Rates of remission continue to increase in the next five years (ranging between 40% and 75%) (20). Some authors have even reported positive effects 15 years after thymectomy (10,16). The type of thymectomy technique also plays a role in this respect. The major differences in remission rates obtained depending on the thymectomy technique used suggests that "the more extensive the thymus resection, the better the results obtained" (20). However, these results must be considered with caution as it is difficult to ascertain whether the symptoms improve as a result of the surgery or due to the natural course of MG, as spontaneous remissions may occur in 10–20% of patients in the long term (9,16).

Advocates of thymectomy as the standard treatment in myasthenia have pointed to observations that thymectomized patients had higher rates of remission and improvement, fewer myasthenic crises and needed less

prednisone and pyridostigmine after surgery than those receiving conservative medical treatment (3-5,9,21). Various thymectomy techniques have been used since Blalock. Many aimed to avoid post-sternotomy scarring, while others aimed to avoid injuries in the recurrent laryngeal, left vagus or the phrenic nerves. Although the objective is to remove as much thymus tissue as possible, complete removal is sometimes impossible, especially in cases with microscopic ectopic thymic tissue foci. According to the MGFA, thymectomies are classified in five groups: T-1 or transcervical thymectomy, T-2 or videoscopic thymectomy, T-3 or transsternal thymectomy, T-4 or transcervical & transsternal thymectomy, and T-5 infrasternal thymectomy. Each operating technique also has several surgical variations; for example, there is the standard technique and the (more aggressive) extended technique for T-3 (transsternal thymectomy). Although resection of the thymus should be as extensive as possible, a comparative analysis of the different resectional techniques is very difficult, as the studies are neither prospective nor controlled, some have design problems and others do not comply with the standard recommendations of the Task Force of the MG Foundation of America (2). In the MGTX trial, the thymectomy technique chosen was Extended Transsternal Thymectomy (T-3b). Removal of almost all the mediastinal tissue, including cervical tissue, is achieved with this technique. This is the most aggressive form of transsternal thymectomy. However, this technique often leaves small amounts of thymus in the neck. Shortcomings in the choice of surgical technique were deemed to be the main cause of persistent incapacitating myasthenic symptoms in patients after thymectomy. In specific terms, incomplete resections, leading to the presence of residual or active ectopic thymic tissue, were accompanied by poor results. Rethymectomy may be justified for these patients. Thoracic surgeons needed to reconsider which of the various thymectomy techniques achieved complete excision of the thymic tissue (13). The number of thymectomies fell dramatically with the appearance of the immunoglobulins, plasma exchange therapy, alternate-day prednisone, azathioprine, cyclophosphamide, cyclosporin A, mycophenolate mofetil, tacrolimus, rituximab and other immunosuppressant drugs in the therapeutic arsenal for treating MG, calling into question whether surgical resection was superior to medical treatment. These controversies over whether patients should undergo surgery or not were based on the fact that all the observations of the effectiveness of thymectomy came from non-randomized controlled trials (i.e., non-class I studies). This criticism is more evident in the meta-analysis performed in four recent reviews of the medical literature. The main objective of these reviews was to assess the efficacy of thymectomy in non-thymomatous MG (17,25-27). More than 500 articles were reviewed, containing data from more than 4,000 patients who underwent surgery. Numerous risks of bias were identified in the design of most of the studies, especially a lack of randomization (class II trial), incomplete follow-up, an absence of blind evaluator investigators, an absence of standardized methods for assessing patient status before and after thymectomy, conflictive clinical classifications of patients, a lack of uniform post-interventional status criteria, different definitions of remission and improvement, and defective statistical methods. Most were retrospective case series or retrospective cohort type studies (class III trials). Others were anecdotal reports and narrative reviews (17,26,27). Given these shortcomings in the study design, the remission rates range from 13.7% to 50.0% and improvement rates range from 46.6% to 93.2%. However, different definitions of remission were used. In many cases of improvement, the authors do not specify whether the thymectomized patients are taking immunosuppressive drugs or cholinesterase inhibitors. As a result, despite the relative risk (RR) of clinical remission, pharmacological remission and improvement rate suggesting the superiority of thymectomy compared to medical treatment, these reports should be considered with caution (17,25-27).

The major confounding factors in the multivariate analysis of the real effects of thymectomy included the patient's age, the disease duration prior to surgery, the choice of surgical technique for maximum removal of thymus tissue, gender, prednisone therapy before and after surgery, doses of pyridostigmine before and after surgery, disease severity, thymus histology, and the possibility of spontaneous improvement during the natural course of the disease (see *Table 1*). As a consequence, comparative analysis of the results of thymectomy remains problematic (28-36).

However, when we analyzed the QMG score results of the MGTX Study Group for the 126 patients randomized between 2006 and 2012, the differences between the two groups were moderate. A difference of 2.84 points was observed (8.99 points in the group of patients with prednisone, versus 6.15 points in the group of patients who had undergone surgery). None of the patients achieved complete stable remission (CSR), one of the MGFA

Table 1 Prognostic factors influencing the post-thymectomy outcome reported in the literature in non-thymomatous adult MG patients

Factor analyzed	Outcome predicted
Younger patients (<35 years)	Good
Symptoms <2 years before operation	Good
Severity of disease. Milder forms responded more rapidly than severe forms, but the improvement seems unrelated to severity in some series	Good
Age >60 years old	Poor
Gender effect. Men have the same likelihood of improvement as females, but some series report better results in women	Controversial
Fast progression to severe symptoms	Poor
Maximum removal of thymus/thymic fat	Good
Presence of residual or active ectopic thymic tissue	Poor
Extended transsternal thymectomy	Good
Unstable MG before surgery	Poor (immediately)
Improvement <3 years post-thymectomy	Good
History of previous thymectomy	Poor
Prednisone *de novo*	Good
High doses of pyridostigmine before operation	Poor
Thymic hyperplasia	Good
Thymic atrophy	Poor
Normalization of elevated CD4–/CD8– T cells	Good
Normalization of elevated CD4+/CD8* T cells	Good
Fall in anti-AChR antibody titers	Good

MG, myasthenia gravis; AChR, acetylcholine receptor.

primary therapeutic objectives in the treatment of MG. The minimal manifestations (MM) category of post-interventional status was achieved by 67% of the surgery group *vs.* 47% of the patients receiving medical treatment alone. The MG therapy status in both branches requires much higher doses of prednisone (44 mg on alternate days in the thymectomized group versus 60 mg on alternate days in the prednisone group) than those habitually used in neuromuscular clinics (37). Whether using other immunosuppressant drugs would have achieved a reduction in the amount of prednisone to consolidate the benefits of thymectomy and reach CSR will never be known (15,35,38).

Another shortcoming of this randomized clinical trial was the fact that it analyzed the results over a three-year period, when most experts believe that post-thymectomy evaluation at 5 years is a good starting point to evaluate remission rates and effectiveness after thymus resection. A further shortcoming is that it includes patients up to 65 years old. There is no rationale for thymectomy in non-thymomatous MG patients aged over 60 years old, as the results are poor, unlike in younger patients (4,5,9,10,19,33,34).

In conclusion, this study provides a partial response to the doubts over the effectiveness of thymectomy that have persisted for the last fifty years. A controlled trial of thymectomy, despite being long overdue, would have the merit of being "better late than never". Future studies could analyze whether any of the subgroups of non-thymomatous MG patients analyzed respond better than the others, or whether the effects of the thymectomy are improved in the fifth year post-surgery (*Table 2*).

Table 2 Questions not analyzed in the MGTX trial

Is the patient's age a factor influencing the outcome of thymectomy?
Role of thymic involution in the response to thymectomy in patients aged over 55 years old
Is thymectomy beneficial only in patients with a short disease duration ?
Do remission rates continue even 5 years post-thymectomy? Is long-term improvement possible after thymectomy?
Role of thymectomy in ocular forms
Correlations between thymic pathology and outcome after thymectomy
Pyridostigmine doses before and afterwards in both arms
Effect of other immunomodulating drugs for consolidation of complete stable remission after thymectomy
How to distinguish the beneficial effects of thymectomy from improvement due to natural history of MG
Investigation of biomarkers for MG in thymus and peripheral blood that could predict the outcome of the thymectomy

MG, myasthenia gravis.

Acknowledgments

Funding: J Gamez is the recipient of a grant from the Spanish Fondo de Investigaciones Sanitarias (FIS PI16-01673-FEDER), and an Interlaken Research Awards Program (2012-12094537).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Xiangya Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2017.01.02). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med 2016;375:511-22.
2. Blalock A. Thymectomy in the treatment of myasthenia gravis. Report of twenty cases. J Thorac Surg 1944;13:316-39.
3. Buckingham JM, Howard FM Jr, Bernatz PE, et al. The value of thymectomy in myasthenia gravis: a computer-assisted matched study. Ann Surg 1976;184:453-8.
4. Papatestas AE, Genkins G, Kornfeld P, et al. Effects of thymectomy in myasthenia gravis. Ann Surg 1987;206:79-88.
5. Durelli L, Maggi G, Casadio C, et al. Actuarial analysis of the occurrence of remissions following thymectomy for myasthenia gravis in 400 patients. J Neurol Neurosurg Psychiatry 1991;54:406-11.
6. Masaoka A. Extended trans-sternal thymectomy for myasthenia gravis. Chest Surg Clin N Am 2001;11:369-87.
7. McQuillen MP, Leone MG. A treatment carol: thymectomy revisited. Neurology 1977;27:1103-6.
8. Rowland LP. Controversies about the treatment of myasthenia gravis. J Neurol Neurosurg Psychiatry 1980;43:644-59.
9. Oosterhuis HJ. Thymectomy in myasthenia gravis. A review. Ital J Neurol Sci 1983;4:399-407.
10. Masaoka A, Yamakawa Y, Niwa H, et al. Extended thymectomy for myasthenia gravis patients: a 20-year review. Ann Thorac Surg 1996;62:853-9.

11. Åhlberg R, Yi Q, Pirskanen R, et al. The effect of thymectomy on autoreactive T- and B-lymphocytes in myasthenia gravis. J Neuroimmunol 1997;74:45-54.
12. Sempowski G, Thomasch J, Gooding M, et al. Effect of thymectomy on human peripheral blood T cell pools in myasthenia gravis. J Immunol 2001;166:2808-17.
13. Jaretzki A, Steinglass KM, Sonett JR. Thymectomy in the management of myasthenia gravis. Semin Neurol 2004;24:49-62.
14. Onodera H. The role of thymus in the pathogenesis of Myasthenia Gravis. Tohoku J Exp Med 2005;207:87-98.
15. Ponseti JM, Gamez J, Azem J, et al. Post-thymectomy combined treatment of prednisone and tacrolimus versus prednisone alone for consolidation of complete stable remission in patients with myasthenia gravis: a non-randomized, non-controlled study. Curr Med Res Opin 2007;23:1269-78.
16. Oosterhuis HJ. editor. Myasthenia Gravis. Groningen: Neurological Press, 1997:122-4.
17. Gronseth GS, Barohn RJ. Thymectomy for Myasthenia Gravis. Curr Treat Options Neurol 2002;4:203-9.
18. Jaretzki A 3rd. Thymectomy for myasthenia gravis: analysis of controversies-patient management. Neurologist 2003;9:77-92.
19. Keesey JC. A history of treatments for myasthenia gravis. Semin Neurol 2004;24:5-16.
20. Sonett JR, Jaretzki A 3rd. Thymectomy for nonthymomatous Myasthenia Gravis. A critical analysis. Ann N Y Acad Sci 2008;1132:315-28.
21. Bachmann K, Burkhardt D, Schreiter I, et al. Thymectomy is more effective than conservative treatment for myasthenia gravis regarding outcome and clinical improvement. Surgery 2009;145:392-8.
22. Barnett C, Katzberg HD, Keshavjee S, et al. Thymectomy for non-thymomatous myasthenia gravis: a propensity score matched study. Orphanet J Rare Dis 2014;9:214.
23. Drachman DB. Myasthenia Gravis. Semin Neurol 2016;36:419-24.
24. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology 2016;87:419-25.
25. Diaz A, Black E, Dunning J. Is thymectomy in non-thymomatous myasthenia gravis of any benefit? Interact Cardiovasc Thorac Surg 2014;18:381-9.
26. Cea G, Benatar M, Verdugo RJ, et al. Thymectomy for non-thymomatous myasthenia gravis. Cochrane Database Syst Rev 2013;(10):CD008111.
27. Luo Y, Pan DJ, Chen FF, et al. Effectiveness of thymectomy in non-thymomatous myasthenia gravis: a systematic review. J Huazhong Univ Sci Technolog Med Sci 2014;34:942-9.
28. Gronseth GS, Barohn RJ. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55:7-15.
29. Jaretzki A 3rd, Aarli JA, Kaminski HJ, et al. Thymectomy for myasthenia gravis: evaluation requires controlled prospective studies. Ann Thorac Surg 2003;76:1-3.
30. Rubin JW, Ellison RG, Moore HV, et al. Factors affecting response to thymectomy for myasthenia gravis. J Thorac Cardiovasc Surg 1981;82:720-8.
31. Monden Y, Nakahara K, Kagotani K, et al. Effects of preoperative duration of symptoms on patients with myasthenia gravis. Ann Thorac Surg 1984;38:287-91.
32. Ashour M. Prevalence of ectopic thymic tissue in myasthenia gravis and its clinical significance. J Thorac Cardiovasc Surg 1995;109:632-5.
33. Téllez-Zenteno JF, Remes-Troche JM, García-Ramos G, et al. Prognostic factors of thymectomy in patients with myasthenia gravis: a cohort of 132 patients. Eur Neurol 2001;46:171-7.
34. Huang CS, Hsu HS, Huang BS, et al. Factors influencing the outcome of transsternal thymectomy for myasthenia gravis. Acta Neurol Scand 2005;112:108-14.
35. Ponseti JM, Gamez J, Vilallonga R, et al. Influence of ectopic thymic tissue on clinical outcome following extended thymectomy in generalized seropositive nonthymomatous myasthenia gravis. Eur J Cardiothorac Surg 2008;34:1062-7.
36. Andersen JB, Erik Gilhus N, Sanders DB. Factors Affecting Outcome in Myasthenia Gravis. Muscle Nerve 2016;54:1041-9.
37. Ropper AH. RetroSternal--Looking Back at Thymectomy for Myasthenia Gravis. N Engl J Med 2016;375:576-7.
38. Ponseti JM, Gamez J, Azem J, et al. Tacrolimus for myasthenia gravis: a clinical study of 212 patients. Ann N Y Acad Sci 2008;1132:254-63.

doi: 10.21037/jxym.2017.01.02

Cite this article as: Gamez J, Ponseti JM. Thymectomy for non-thymomatous myasthenia gravis: the end of controversy, albeit fifty years late. J Xiangya Med 2017;2:4.

