Thymectomy for Myasthenia Gravis: Complete Stable Remission and Associated Prognostic Factors in Over 1000 Cases

Andrew J. Kaufman, MD,[*] Justin Palatt, MD,[*] Mark Sivak, MD,[†] Peter Raimondi, BS,[*] Dong-Seok Lee, MD,[*] Andrea Wolf, MD, MPH,[*] Fouad Lajam, MD,[*] Faiz Bhora, MD,[*] and Raja M. Flores, MD[*]

The efficacy of thymectomy and the optimal surgical technique in the treatment of myasthenia gravis (MG) remain controversial. Long-term outcomes are lacking and remission rates are based on small populations. We reviewed our institutional experience of thymectomy for MG focusing on long-term outcomes, complete stable remission (CSR), improvement of symptoms, after transcervical, transsternal, thoracotomy, and VATS thymectomy. A retrospective review of a prospectively maintained database of 3017 patients from 1941-2013 with MG was performed. Patients who underwent thymectomy with follow-up data including age at the time of surgery, sex, date of onset of symptoms, date of surgery, Osserman classification before and after surgery, surgical technique, date of remission, and status at last follow-up were included in the analysis. CSR and prognostic factors were analyzed by crude rate, Kaplan-Meier estimate, chi-squared test, Wilcoxon test, and a Cox proportional model. Overall, 1002 thymectomy patients with complete data were analyzed, and 35.5% ($n = 355$) derived benefit from surgery. Crude rate CSR was 19% ($n = 191$) and an additional 16% ($n = 164$) symptomatically improved requiring less medication after thymectomy. Also, 58% ($n = 580$) were stable after resection, and 6.7% ($n = 67$) developed progressive disease. Kaplan-Meier estimates of CSR were 27.7%, 36.7%, and 47.3% at 10, 25, and 40 years, respectively. On multivariate analysis, transsternal technique, thymoma, and preoperative Osserman classification were significantly associated with failure to achieve CSR. Thymectomy provides long-term CSR in 47.3% of patients with long-term follow-up. Patients with MG should be offered thymectomy when possible.

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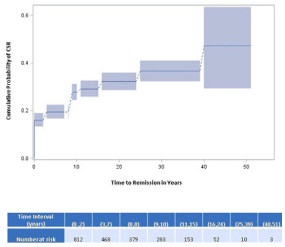

Kaplan-Meier graph with interval censoring—time to remission after thymectomy

Central Message

Thymectomy for myasthenia gravis results in significant long-term complete stable remission and improvement of symptoms.

Perspective Statement

This is the largest, single center, retrospective analysis of the outcomes of thymectomy for the treatment of myasthenia gravis published to date. Our long-term data suggest that thymectomy provides a significant chance of achieving complete stable remission in many patients. Thymectomy should be considered for the treatment of myasthenia gravis, especially in those with mild symptoms.

See Editorial Commentary on pages 572-573.

INTRODUCTION

Myasthenia gravis (MG) is a rare autoimmune disease that frequently causes severe disability and can become life threatening. Generalized MG has been successfully treated with anticholinesterases, immunosuppressant medications, and surgery for many years. Thymectomy for MG was first described by Schumacher and Roth in 1913 and later popularized by Blalock et al[1] in 1939 when he described a durable remission of severe generalized MG in a 19-year-old woman following thymectomy for a cystic thymic tumor. Blalock's subsequent series describing symptomatic improvement in patients with nonthymomatous MG following thymectomy further established this treatment.[2] Since then a preponderance of retrospective, nonrandomized or controlled studies have described thymectomy as an effective treatment for MG.[3] However, the role of thymectomy in the management of MG

[*]Department of Thoracic Surgery, Mount Sinai Health System, Icahn School of Medicine, New York, NY
[†]Department of Neurology, Mount Sinai Health System, Icahn School of Medicine, New York, NY

Address reprint requests to Raja M. Flores, MD, Department of Thoracic Surgery, Mount Sinai Health System, Icahn School of Medicine, One Gustave L. Levy Place, Box 1023, New York, NY 10029. E-mail: raja.flores@mountsinai.org

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remains controversial because of the lack of a definitive randomized controlled trial comparing thymectomy to nonsurgical management, the prevalence of studies using small sample sizes, differing definitions of remission and severity of symptoms, short duration of follow-up, and less-rigorous statistical analyses. Furthermore, multiple studies have reported widely divergent rates of complete stable remission (CSR) following surgery.[4] Many other studies have provided inconsistent associations of favorable or unfavorable variables associated with CSR including patient age and sex,[5,6] duration and severity of preoperative symptoms,[5,7-11] surgical technique,[8,9,12-14] extent of resection,[15,16] and the presence of thymoma.[17-19] A recent meta-analysis of 28 published reports of outcomes of thymectomy in MG that included 8490 patients from 21 MG cohorts indicated that patients were twice as likely to achieve CSR, 1.7 times more likely to have symptomatic improvement, and 1.6 times more likely to be asymptomatic.[3] Our present study was specifically conducted to analyze the long-term outcomes of thymectomy for MG in a large number of patients, more accurately describe the rate of CSR, and to define the patient characteristics significantly affecting postthymectomy CSR.

PATIENTS AND METHODS

Patient Selection

A retrospective review of a prospectively maintained database of patients treated at the Myasthenia Gravis Clinic of Mount Sinai Hospital was performed. From 1941-2013, a total of 3017 patients were entered into the patient registry. The Institutional Review Board of the Icahn School of Medicine at the Mount Sinai Health System approved the study. Of the 3017 patients in the registry, the majority were treated medically without thymectomy. Data regarding the medications and doses of medications prescribed to these patients were incomplete, and these patients were excluded from the study. Only patients who underwent thymectomy were selected for review. Patient data including age at the time of surgery, sex, date of onset of symptoms, date of surgery, Osserman classification before and after surgery, surgical technique, the date of remission, and the status at last follow-up were included in our analysis. A total of 1002 thymectomy patients were identified, 30% of all records, and were selected for our study.

Follow-Up

Neurologists with expertise in MG confirmed the diagnosis, assigned the Osserman classification, and recorded patient characteristics. Patient data were originally recorded in paper form and later converted retrospectively into an electronic database, or prospectively added after its creation by a single data coordinator and maintained until the time of this study. The timing of follow-up visits and the collection of data was based on physician preference without a standardized protocol. Data were entered directly into the chart or the database by the data coordinator after each visit. The severity of patient symptoms was graded using a modified Osserman classification system because it was most commonly applied to patients in the prospective database. The modified Osserman classification of severity of symptoms classified ocular symptoms as class I, mild generalized weakness as class II, moderate generalized weakness as class III, and severe generalized weakness or respiratory dysfunction or both as class IV. In patients with multiple preoperative Osserman classification assignments, the most severe recorded preoperative classification was assigned to the patient and used in our analysis. We chose the maximum severity of symptoms documented before surgery as the patient's final classification because it likely represented the most complete extent of the patient's illness and reduced the possibility that preoperative treatments given in preparation for surgery that could spuriously reduce the patient's Osserman classification.[19,20] The more detailed Myasthenia Gravis Foundation of America clinical classification and quantification score for disease severity was not available for most patients. Patients who were classified using an alternative system were retroactively reclassified to fit the modified Osserman classification to allow for consistent analysis.

Surgical Approach

Patients were divided into cohorts based on the technique of surgical thymectomy. Thymectomy procedures were recorded as transcervical, transsternal, thoracotomy, or video-assisted thoracoscopic surgery (VATS), based on the surgical approach used, not by the extent of the mediastinal or cervical resection. The standard transsternal, thoractomy, and VATS resections performed at our institution included removal of the entire encapsulated thymus including the cervical poles, the mediastinal fat located between the thyroid gland cranially and the diaphragm caudally, and between the phrenic nerves laterally. Transcervical resections consisted of both en bloc removal of all thymic and perithymic tissue and enucleation of thymus without perithymic tissue depending on 2 surgeon's preference, without a sternal split. Extended