Active ectopic thymus predicts poor outcome after thymectomy in class III myasthenia gravis

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Objective: The presence of ectopic thymic tissue has been considered one of the most significant predictors of poor outcome after thymectomy for myasthenia gravis, but the role of active ectopic tissue is unknown. The current study analyzed the importance of this factor on post-thymectomy outcome of patients with class III myasthenia gravis.

Methods: We retrospectively reviewed 106 patients with class III, anti-acetylcholine receptor antibody-positive, nonthymomatous myasthenia gravis (70 female, 36 male; mean age, 41 ± 17 years) who underwent transsternal extended thymectomy between 1980 and 2005. Quality of life was assessed from 1996 with the Short Form 36 questionnaire. Prognosticators were investigated using complete stable remission and normalized component summaries as end points.

Results: Major morbidity rate was 5% with no perioperative mortality. Ectopic thymic tissue was detected in 51 patients (48%), 34 of whom (67%) presented germinal centers. Complete follow-up was available in 96 patients (mean 160 ± 91 months). Fifty-two patients (54%) achieved complete stable remission, and 20 patients (21%) presented clinical and pharmacologic improvement. Lack of postoperative improvement in physical and psychosocial domains was significantly correlated with active ectopic thymus. At Kaplan–Meier evaluation, duration of symptoms (>12 months) ($P = .04$), oropharyngeal involvement ($P = .02$), germinal centers ($P = .03$), ectopic thymus ($P = .001$), and active ectopic thymus ($P < .0001$) were negative predictors of complete stable remission. The presence of active ectopic thymus was the most significant negative predictor of complete stable remission at Cox regression ($P = .03$).

Conclusions: Extended thymectomy yields good outcome in patients with nonthymomatous class III myasthenia gravis. The presence of active ectopic thymus was the most significant predictor of poor outcome. These patients should be rigorously followed and undergo early aggressive therapy. (J Thorac Cardiovasc Surg 2012;143:601-6)

GTS

The removal of as much thymic tissue as possible is considered one of the key points for predicting complete stable remission (CSR) of nonthymomatous myasthenia gravis (MG).[1-7] The persistence of ectopic thymic tissue[8-11] is deemed as one of the main reasons of poor outcome after thymectomy.[12,13] Furthermore, the presence of germinal centers in the thymus has reported to be a source of antibodies against acetylcholine receptors (anti-AchR Ab) and another significant negative prognostic factor.[12,13]

We hypothesized that the histologic evidence of active tissue in both native and ectopic thymus could predispose to the failure of a symptomatologic response to thymectomy. The purpose of our retrospective study was to analyze the most significant predictor of poor outcome after thymectomy in class III nonthymomatous MG, with special attention to the presence of germinal centers in heterotopic thymus.

PATIENTS AND METHODS

Patients

Of a total of 194 myasthenic patients who underwent transsternal extended thymectomy at Tor Vergata University between 1980 and 2005, we retrospectively reviewed 106 patients affected with nonthymomatous, anti-AchR Ab–positive, class III MG (Figure 1). According to the Myasthenia Gravis Foundation of America (MGFA), class III was identified as a moderate weakness predominantly affecting limb or axial muscles (type a) or oropharyngeal muscles (type b).[14] Patients operated before 2000 and therefore classified according to the Osserman's classification[15] were retrospectively reclassified. We restricted the study only to this class because it is the most common and fittest to detect significant quality of life changes. We also excluded patients operated after 2005 to have a minimum follow-up of at least 5 years. Patient population consisted of 70 female and 36 male subjects aged 15 to 74 years (mean, 41.1 ± 16.6 years). Further demographic data are summarized in Table 1. Permission for activating the entire project, including the use of medical records and specimen reanalysis, was issued by the internal review board of Tor Vergata University. Each patient released written and fully informed consent to the use of personal data.

The diagnosis of MG was based on clinical features and 1 or more of the following criteria: response to edrophonium chloride, positive electromyography, and demonstration of circulating anti-AchR Ab. A quantitative MG score[16] from 0 (no impairment) to 39 (maximum impairment) was also evaluated pre- and postoperatively.

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Abbreviations and Acronyms

anti-AchR Ab = antibodies against acetylcholine receptors
CI = confidence interval
CSR = complete stable remission
MCS = mental component summary
MG = myasthenia gravis
MGFA = Myasthenia Gravis Foundation of America
PCS = physical component summary
SF-36 = Short Form 36

Before thymectomy, all patients were receiving anticholinesterase drugs alone or in combination with steroids (n = 28). Only 5 patients were also taking azathioprine. A medical panel composed of neurologists, thoracic surgeons, and anesthesiologists discussed the decision and timing for thymectomy. Each patient was clinically stable before surgery. In the presence of increasing weakness or bulbar symptoms, plasmapheresis (n = 17) or intravenous immunoglobulins (n = 27) were administrated before surgery.

Surgical Technique

We consider thymectomy extended according to Sonnet and Jaretzki.[17] The operation was accomplished under general anesthesia with single-lung ventilation. Only short-acting, nondepolarizing neuromuscular relaxants were occasionally used. During the operation and 12 hours after, oral pyridostigmine was administered through a nasogastric tube. Resection routinely included areas more frequently the site of ectopic thymic tissue,[2] such as perithymic fat tissue from anterior mediastinum, neck, aortocaval groove, aortopulmonary window, retroinnominate space, and both cardiophrenic angles.

At the end of the operation, we encouraged early extubation and physiotherapy. Pain control was preferably restricted to oral analgesics.

Thymic Specimen Evaluation

All excised tissue was routinely examined. Hematoxylin and eosin–stained sections were prepared from paraffin-embedded blocks and examined under low magnification (×20). Where histologic data were missing, the specimens were reprocessed by retrieving them from archive material.

Ectopic thymus was researched by randomly taking 1 from every 5 sections of fat tissue inclusion collected during thymectomy. The presence of the germinal centers was researched by examining visual fields of at least 5 sections of the thymus. Monoclonal antibodies against CD23 were used to demonstrate the presence of germinal centers. Briefly, sections from each specimen were cut at 3 to 5 μm, mounted on glass, and dried overnight at 37°C. All sections were then deparaffinized in xylene, rehydrated through a graded alcohol series, and washed in phosphate-buffered saline. This buffer was used for all subsequent washes and for dilution of the antibodies. Tissue sections were heated twice in a microwave oven for 5 minutes each time at 700 W in citrate buffer (pH 6) and then processed with the standard streptavidin-biotin-immunoperoxidase method. Mouse monoclonal anti-human antibodies specific for CD23 (clone 1B12, Novocastra, UK) were used at a 1:100 dilution. All the primary antibodies were incubated for 1 hour at room temperature. Diaminobenzidine was used as the final chromogen, and hematoxylin was used as the nuclear counterstain. Negative controls for each tissue section were performed leaving out the primary antibody. Cytoplasmic staining with anti-human CD23 was scored as positive by an experienced pathologist.

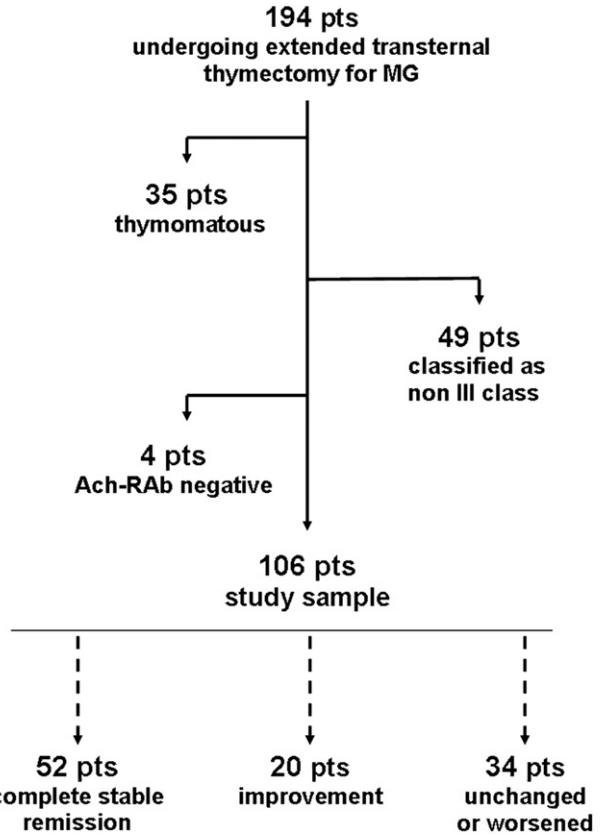

FIGURE 1. Diagram indicating patient's selection. *Pts,* Patients; *MG,* myasthenia gravis; *Ach-RAb,* acetylcholine receptor antibodies.

Postoperative Evaluation

Clinical outcome was always assessed according to the MGFA postintervention status classification[14] during a multidisciplinary follow-up session. CSR was defined as no symptoms or sign of MG at careful examination for at least 1 year in the absence of therapy during that time.[14]

Since 1996, quality of life changes after surgery were measured by the Medical Outcomes Study Short Form 36 (SF-36) self-administered questionnaire.[18] The SF-36 consists of 36 multiple-choice questions covering 8 health concepts: physical functioning, social functioning, physical role, emotional role, vitality, body pain, mental health, and general health perception (best score = 100, worst = 0). From these values, it is also possible to calculate a unique score for the physical component summary (PCS) and the mental component summary (MCS) (Health Assessment Laboratory, New England Medical Center, Boston, Mass, 1994). We repeated the same preoperative evaluations 6 months after thymectomy and then every 12 months after.

Statistical Analysis

We presented values of descriptive variables as mean ± standard deviation. All analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Ill). The interdependence between prognostic factors and end points was tested by the 2-tailed chi-square test. End points were the improved postintervention status, normalized (≥50) PCS values, and normalized (≥50) MCS values. Significant variables were then analyzed with logistic regression. Correlations between continuous variables were analyzed by the Spearman test.

CSR survival was determined by the Kaplan–Meier method. Time to CSR was defined as the time between the day of surgery and the date of CSR. Patients who had not achieved CSR were censored with time to