Thymectomy in myasthenia gravis

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Myasthenia gravis (MG) is a potentially serious but treatable autoimmune disorder of the neuromuscular junction characterized by skeletal muscle weakness and is a disease of young women and old men. The overall incidence rate of MG has been constant and is estimated at 2.1 to 5.0 per 100,000 people per year. However, the prevalence has increased over time with recent estimates approaching 20 per 100,000 in the US population. There is a dramatic decrease in the mortality rate from 30% in the mid-1950s to 3% in the late 1990s. In the US Nationwide Inpatient Sample database, the overall in-hospital mortality was 2.2%, being higher in MG crisis (4.47%). Older age and respiratory failure were the predictors of death.

Current therapies in autoimmune MG aim to restore the available acetylcholine receptors deplete the autoantibodies or suppress the immune system. To achieve these goals, thymectomy is one of the options among different treatment strategies. The presumed role of the thymus in MG has provided theoretical justification for the procedure. Abnormalities of the thymus gland are common in patients with MG; thymoma is present in 10-15% of patients and lymphoid follicular hyperplasia in about 70%. In older patients, normal involution of the thymus gland produces thymic atrophy. In addition thymus plays an important immunopathological role in the development of autoimmune MG. The exact mechanism by which thymectomy produces benefits in MG is uncertain. The possible mechanisms include: (1) removal of the thymus may eliminate a source of continued antigen stimulation; (2) thymectomy may remove a reservoir of B cells secreting acetylcholine-receptor antibody; and (3) thymectomy may in some way correct a disturbance of immune regulation in MG.

The use of thymectomy in generalized autoimmune MG is on the basis of circumstantial evidence and expert opinion. A systematic review of 21 retrospective thymectomy studies with 8490 patients suggested that patients having thymectomy were two times more likely to experience improvement than those who did not have this intervention. The improvement was defined as medication-free remission, asymptomatic on medication, or improved on medications. The median rates of each category of improvement were remission 25%, asymptomatic 39%, or clinically improved 70%. However, significant confounding differences in baseline characteristics of prognostic importance existed between thymectomy and nonthymectomy patient groups. Based on these results thymectomy is recommended in patients with nonthymomatous MG as an option to increase the probability of remission or improvement. However, the effect of thymectomy is usually not apparent until after one year, and the full effect is not felt for five years.

Retrospective series have shown lower response rates of thymectomy in older subjects and the complications are likely to be greater. In a recent study of thymectomy in nonthymomatous MG, anti-MuSK positivity correlated with poor response to operation. In another non-randomized, non-controlled study thymectomy seems to be less effective in seronegative anti-MuSK-positive MG.
Thymomatous MG is an absolute indication for thymectomy. Thymoma occurs in approximately 10-15% of patients with MG[12,13] and MG occurs in approximately 33% of patients with thymoma.[24] A large cohort study of thymoma and MG suggests that thymoma with MG is equally and less malignant than that without MG,[25] whereas earlier studies have reported that the presence of MG in thymoma patients is an indicator of poor prognosis.[26-28] Completeness of resection is the most commonly cited statistically significant prognostic factor in thymoma. The effect of complete resection in most of the series was an approximately 50% increase in survival at five years. The use of surgery as the sole therapeutic maneuver in thymoma depends on the stage considered.[29] The outcome predictors of nonremission of MG after thymectomy in patients with thymomatous MG include thymic carcinoma (Müller-Hermelink system), age more than 55 years, and interval from the onset of symptoms to thymectomy of less than one year.[30] Hsu et al.[31] suggest that thymoma is associated with relapse of symptoms after transternal thymectomy for MG. In their series, a significantly greater number of patients in the thymomatous group had relapse of symptoms than in the nonthymomatous group after complete remission was achieved.

In conclusion the balance of evidence currently favors thymectomy for generalized nonthymomatous MG (level of evidence 2; recommendation grade B).[21] In the absence of thymoma, the current practice is generally not to recommend thymectomy for patients over age 60 (level of evidence 3; recommendation grade D).[21] Thymectomy is mostly considered scarcely effective in anti-MuSK-positive MG; however, at present, no firm conclusions can be drawn on its role in the treatment of this form of MG.[22,23,32] In thymomatous MG, thymectomy should always be performed. The low chance of achieving remission in thymoma-associated MG underlines the importance of an early diagnosis as well as the need for more aggressive therapeutic strategies.[33]

The other area of controversy in thymectomy for MG is the preferred surgical approach. The surgical approaches to thymectomy are varied. Myasthenia Gravis Foundation of America (MGFA) has broadly classified the surgical techniques of resection based on the operative approach and extent of surgical resection: T-1. Transcervical thymectomy (a. basic, b. extended); T-2. Videoassoscopic thymectomy (a. video-assisted thoracoscopic surgery thymectomy (VATS), b. video-assisted thoracoscopic extended thymectomy VATET); T-3. Trans-sternal thymectomy (a. standard, b. extended); and T-4. Transcervical and trans-sternal thymectomy.[34,35] The other evolving surgical techniques include robotic approaches (T-2.a) and bilateral thoracoscopic approaches (T-2.b). Overall individual case series have reported data that support the validity and success of all the approaches.[18] In this issue Toolabi et al.[36] have reported the advantages of VATS in generalized nonthymomatous MG. However, the types of thymectomy have not been compared directly in any randomized study and there is insufficient evidence to determine which thymectomy technique is superior in the management of MG.[37] Autoimmune MG varies substantially in its clinical presentation. The clinical subgroups include: Early-onset MG (< 40 years, anti-AchR-antibodies, thymic hyperplasia), late-onset MG (> 40 years, normal thymus, anti-AchR-antibodies, antibodies to titin, ryanodine receptors), thymomatous MG (thymoma, anti-AchR antibodies, antibodies to titin, ryanodine receptor, KCNA4), anti-MuSK MG (anti-MUSK antibodies, normal thymus), anti-AchR and anti-MuSK-negative MG (seronegative generalized MG, thymic hyperplasia, antibodies against clustered AchR in 66%), and ocular MG (anti-AchR antibodies in 50%). Accumulating evidence suggests that clinical MG subgroups might respond differently to treatment.[15,16] An early thymectomy is an option on the basis of circumstantial evidence and expert opinion in nonthymomatous sero-positive MG aged 18-50 years and with generalized weakness. Thymectomy seems to be less effective in sero-negative anti-MuSK-positive MG than in anti-MuSK-negative MG. In the very young and the elderly the current practice is generally not to recommend thymectomy. In thymomatous MG, thymectomy should always be performed. The low chance of achieving remission in this subgroup underlines the importance of an early diagnosis as well as the need for more aggressive therapeutic strategies.

Following the publication of the metaanalysis results there seems a significant decline in the rates of thymectomy.[39] In the US Nationwide Inpatients Sample (NIS) the rate of thymectomy has decreased from 7% to 1.5% during 2005.[3] Till date no randomized controlled studies have been done to establish conclusively the benefit of thymectomy in generalized nonthymomatous MG. Currently, a multicenter trial, “Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy”, is ongoing to determine if the surgical procedure, extended transternal thymectomy, combined with prednisone therapy is more beneficial in treating individuals with nonthymomatous MG than prednisone therapy alone.[38] Hopefully, this study may give some conclusive evidence for thymectomy in nonthymomatous MG subgroups.