Long-Term Outcome and Factors Influencing the Outcome of Thymectomy for Myasthenia Gravis

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Thymectomy has gained widespread acceptance as a treatment for patients with myasthenia gravis (MG). Patients with myasthenia gravis who had undergone thymectomy by extended transsternal approach between 1981 and 1987 were retrospectively reviewed to evaluate the result of thymectomy, time to remission, time to maximum improvement and factors influencing remission after thymectomy. There were 128 patients, 45 men and 83 women and the mean ages at the time of thymectomy were 35.7 and 32.2 years respectively. After thymectomy, 41.2% of the patients were in remission, 53% improved and 5.8% had no response. The remission rates at 1, 2, 5 and 10 years after thymectomy were 9%, 17%, 37% and 53% respectively and the median time to remission was 9 years. The maximum improvement rates at 1, 2, 5 and 10 years after thymectomy were estimated to be 30%, 40%, 57% and 78% respectively and the median time to maximum improvement was 3.6 years. Patients with ocular MG, longer duration of symptoms before thymectomy and atrophic thymus gland appeared to take longer to achieve remission although none of the factors was significantly associated with the time to remission. Thymectomy is beneficial for MG patients with satisfactory remission and improvement rates. It is recommended that thymectomy should be advocated for these patients early in the course of the disease because the duration of the symptoms appeared to be the main determinant of the outcome.

Keywords : *Myasthenia gravis, Thymectomy, Outcome, Remission, Improvement*

J Med Assoc Thai 2004; 87(10): 1172-5
e-Journal: *http://www.medassocthai.org/journal*

Thymectomy, whether the patients have thymoma or not, has gained widespread acceptance as a treatment for patients with myasthenia gravis (MG). Studies indicate that patients undergoing thymectomy are more likely to achieve medication-free remission, become asymptomatic and improve compared with patients treated medically. The thymectomized patients were twice as likely to have medication-free remission and 1.6 times as likely to become asymptomatic[1]. The goal of thymectomy as a treatment for MG is to induce remission or at least improvement, permitting a reduction in the requirement for immunosuppressive medication. There is now a broad consensus that patients with generalized MG who are between the ages of puberty and 60 should have thymectomy. Thymectomy in patients older than 60 is also safe and effective [2,3]. The benefits of thymectomy are usually achieved months to years after surgery. The objectives of this study were to present the long-term outcome of MG patients after thymectomy by estimating the probability of remission and maximum improvement and to identify the factors that influence remission time.

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Patients and Method

A cohort of MG patients who had undergone thymectomy by extended transsternal approach between 1981 and 1987 was retrospectively reviewed. The long-term outcomes (i.e., time to remission and

time to maximum improvement after thymectomy) were evaluated. Complete remission was defined as no symptoms and signs without medication and partial remission was defined as no symptoms and signs with a minimal amount of anticholinesterase (Mestinon) alone (not more than 2 tablets of 60 mg a day). Improvement was divided into asymptomatic with immunosuppressive and a minimal anticholinesterase (no symptoms and signs with prednisolone more than 2 tablets of 5 mg a day and Mestinon not more than 2 tablets a day), marked improvement (Osserman grade 1 with prednisolone more than 2 tablets of 5 mg a day and/or Mestinon not more than 4 tablets a day), moderate improvement (improvement of Osserman grading at least 1 grade) and slight improvement (no change in Osserman grading with decrease of doses of drugs). Maximum improvement was defined as the best clinical status of the patients after thymectomy during the follow-up period. Study variables were extracted from the medical records and included sex, age at thymectomy, Osserman grading before and after thymectomy, duration of disease from onset to thymectomy, medication and drug dosage taken before and after thymectomy, pathology of thymus gland, associated underlying diseases and post-operative complication of thymectomy. Survival analysis using the Kaplan-Meier method was used to estimate the probability of remission and the probability of maximum improvement. The log-rank test was used to determine the probability of each variable. P value less than 0.05 was considered statistically significant.

Results

There were 128 MG patients included in the analysis. Eighty-three (65%) were females with a mean age at time of thymectomy of 35.7 years for males and 32.2 years for females. About half of the patients (52%) had a duration of symptoms from disease onset to thymectomy of > 1 year. Seventeen patients (13.3%) also had thyroid diseases (8 hyperthyroidism, 6 non-toxic goiter and 3 Hashimoto's thyroiditis). Median follow-up time was 3.5 years. Most histological findings of thymus glands were hyperplasia (69.5%) followed by thymoma (12.5%) and atrophy (6%). Osserman grading of most patients before thymectomy was IIb (78, 61%), whereas most patients (72, 56%) were normal after thymectomy. Prior to surgery, two-thirds of the patients took Mestinon alone at 6 (range 3-9) tablets/day and one-third of them took prednisolone and Mestinon 7 (range 4-11) and 6 (range 3-9) tablets/day, respectively.

Fifty-three patients (41.3%) were in disease remission with 33 (25.7%) and 20 (15.6%) being in complete and partial remission respectively. As described in Table 1, the overall remission rate was 8/100 person-years. The remission rates at 1, 2, 5 and 10 years were 9% (95% CI: 5.1, 16.7), 17% (95% CI: 10.8, 25.8), 37% (95% CI: 27.7, 47.5) and 53% (95%CI: 42.5, 64.0) respectively. The median time to remission was 9 years. The estimated maximum improvement rates are described in Table 2. At 1, 2, 5 and 10-year maximum improvement rates were 30% (95% CI: 22.8, 39.0), 40% (95% CI: 31.9, 49.3), 57% (95% CI: 48.5, 66.1) and 78% (95% CI: 69.8, 84.7) respectively. The median time to maximum improvement was 3.6 years.

As regards the influencing factors, it appeared that the longer the duration of disease before the operation, the longer it took to achieve remission. It also showed that it took a longer period to get remission in patients with ocular MG and MG with respiratory failure as compared to generalized MG without respiratory failure. It also took the patients with atrophic thymus longer to get remission. However, none of the factors was significantly associated with the time to remission as assessed by the log-rank test (Table 3).

Table 1. Remission rate after thymectomy in myasthenia gravis according to time

Time after thymectomy (years)	Percentage of remission rate (95%CI)
1	9 (5.1-16.7)
2	17 (10.8-25.8)
5	37 (27.7-47.5)
9	50 (39.9-61.2)
10	53 (42.5-64.0)
Overall remission rate	8% per year

Table 2. Maximum improvement rate after thymectomy in myasthenia gravis according to time

Time after thymectomy (years)	Percentage of maximum improvement rate (95%CI)
1	30 (22.8-39.0)
2	40 (31.9-49.3)
3.6	50 (41.7-59.5)
5	57 (48.5–66.1)
10	78 (69.8-84.7)
Overall maximum improvement rate	18% per year

Table 3. Factors influencing the median time to remission after thymectomy

Factors	Median remission time (years)	P-value
Age group (years)		
< 25	4.1	
26-45	11.3	0.202
>46	9.8	
Gender		
Male	10.3	0.799
Female	7.9	
Osserman grading		
I	12.7	
IIa	6.2	0.809
IIb	8.9	
III+IV	11.3	
Treatment before thymectomy		
Prednisolone	5.9	
Mestinon	17.3	0.809
Prednisolone+Mestinon	17.2	
Duration of symptoms (months)		
< 6	6.3	
6-12	7.8	0.533
>12	10.3	
Pathology of thymus		
Hyperplasia	8.0	
Atrophy	18.6	0.528
Thymoma	11.3	
No pathology	11.3	

Discussion

In the present study, 41.2% of the MG patients were in remission, 53% had improved and 5.8% had no response following thymectomy. These results are considered satisfactory and comparable to the response rates of other studies. The remission and improvement rates of these studies varied from 21-47% and 42-62% respectively[4-11]. The authors agree with most investigators that thymectomy is an effective treatment for MG patients. Most of the cases had long standing remission or improvement. The median time to achieve remission after thymectomy was 9 years, the overall remission rate after thymectomy was 8/100 person-years and the overall 5-year remission probability was 37%. The median time to achieve maximum improvement after thymectomy was 3.6 years, the overall maximum improvement rate was 18/100 person-years and the overall 5-year improvement probability was 57%. This demonstrated that most patients' symptoms were progressively improved with time after thymectomy as also observed by others[5,12]. This was most likely to be attributable to thymectomy and not to the natural history of myasthenia gravis itself in view of the progressive nature of the disease. However, it took quite some time to achieve the goal. In conclusion, thymectomy appears to be beneficial for MG patients with satisfactory remission and improvement rates. Patients with ocular MG, longer duration of symptoms before thymectomy (> 1 year) and atrophic thymus gland appeared to take longer to achieve remission but none of the factors showed significant association with the time of remission. Nevertheless, it is recommended that thymectomy should be advocated for MG patients early in the course of the disease because the duration of the symptoms is often the main determinant of the outcome.

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ผลระยะยาวของการผ่าตัดต่อมไทมัสและปัจจัยที่มีผลต่อผลการผ่าตัดในผู้ป่วยโรคมัยแอสทีเนียแกรวิส

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การผ่าตัดต่อมไทมัสเป็นวิธีรักษาโรคมัยแอสทีเนียแกรวิสที่เป็นที่ยอมรับกันทั่วไป ผู้นิพนธ์ได้ศึกษาผู้ป่วยมัยแอสทีเนียแกรวิสที่ได้รับการผ่าตัดระหว่างค.ศ. 1981-1987 เพื่อประเมินผลการผ่าตัด ระยะเวลาจากการผ่าตัดถึงเวลาที่หายจากโรค ระยะเวลาจากการผ่าตัดถึงเวลาที่ดีขึ้นเต็มที่และปัจจัยที่มีผลต่อการผ่าตัด ผู้ป่วยที่ศึกษามีทั้งหมด 128 คน เป็นผู้ชาย 45 คนและผู้หญิง 83 คน โดยมีอายุเฉลี่ย 35.7 และ 32.2 ปีตามลำดับ หลังผ่าตัดผู้ป่วยร้อยละ 41.2 หายเป็นปกติ ร้อยละ 53 ดีขึ้นและร้อยละ 5.8 ไม่เปลี่ยนแปลง อัตราการหายจากโรคที่ระยะเวลา 1, 2, 5 และ 10 ปีหลังผ่าตัดเท่ากับร้อยละ 9, 17, 37 และ 53 ตามลำดับโดยเวลามัธยฐานถึงการหาย 9 ปี อัตราการดีขึ้นที่ระยะเวลา 1, 2, 5 และ 10 ปีหลังผ่าตัดคิดได้ร้อยละ 30, 40, 57 และ 78 ตามลำดับโดยเวลามัธยฐานถึงการที่ดีขึ้น 3.6 ปี ผู้ป่วยที่เป็นเฉพาะที่ตา ผู้ที่เป็นระยะเวลานานก่อนผ่าตัดและผู้ที่ต่อมไทมัสฝ่อ กว่าจะดีขึ้นใช้เวลานานกว่า แต่ไม่มีปัจจัยใดที่มีความสัมพันธ์กับเวลาที่หายจากโรคอย่างมีนัยสำคัญ การตัดต่อมไทมัสได้ผลดีในผู้ป่วยมัยแอสทีเนียแกรวิสและแนะนำให้ผ่าเมื่อเริ่มมีอาการใหม่ ๆ เพราะระยะเวลาที่เป็นโรคก่อนผ่าตัดมักเป็นปัจจัยสำคัญต่อผลของการผ่าตัด