Outcome of thymectomy in myasthenia gravis patients at Neurological Institute of Thailand

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Abstract

Background & Objective: Myasthenia gravis is the most common neuromuscular junction disorders and is caused by autoantibodies against acetylcholine receptors at the postsynaptic muscle endplate. Although thymectomy is current standard treatment but the benefit in long-term outcomes and in non-thymomatous generalized MG patients with negative AChR antibody are still unclear. The objective is to determine the treatment outcomes of thymectomy in non-thymomatous generalized MG patients with or without AChR antibody and identify features related to remission.

Methods: Retrospective chart review of the patients diagnosed with non-thymomatous generalized MG from January 1st, 2014 to December 31st, 2018. Patients were classified into two groups: patients with thymectomy (thymectomy group) and patients with no thymectomy (medication group).

Results: Seventy-six patients were included. All baseline clinical features, investigations and treatment response were compared. At 6 and 12 months follow up, most patients in both groups had a good response to treatment. At 24 months follow up, ratio of patients in thymectomy group with complete stable remission is higher than in medication group (25% vs. 7.5%) and all patients in this group had positive acetylcholine receptor antibody. The patients in thymectomy group required lower dosage of prednisone, azathioprine and cholinesterase inhibitors than in medication group.

Conclusion: Thymectomy was associated with a high probability of achieving remission, reduced cholinesterase inhibitors and immunosuppressive drugs when compared to medication group. Therefore, thymectomy should be strongly considered for non-thymomatous generalized MG patient with positive AChR antibody; and may be considered in non-thymomatous generalized MG patients with negative AChR antibody.

Keywords: Myasthenia gravis, thymectomy, AChR antibody, treatment outcome, remission

INTRODUCTION

Myasthenia gravis (MG) is the most common neuromuscular junction disorders and is caused by autoantibodies against acetylcholine receptor (AChR) in the postsynaptic muscle endplate. The most common presenting symptom is ocular muscle weakness resulting in fluctuating, fatigable, usually asymmetric ptosis and diplopia. During the clinical course, symptoms remain limited to the ocular muscles (ocular myasthenia gravis) in fifty percent of MG patients. In the rest of the patients, symptoms extend to bulbar, limb, axial, and ventilatory muscles, resulting in generalized muscle weakness (generalized myasthenia gravis). In Thailand, prevalence of MG has increased over time with recent estimates approaching 2.17 per 100,000 population. MG associated with a thymoma in some patients. Ten percent of generalized MG patients have thymoma and AChR antibody positivity. Thirty percent of patients with thymoma develop MG and 15% of patients with thymoma have AChR antibody without symptoms of MG. Thymic hyperplasia is a common finding in myasthenia gravis patients. Treatment of MG consists of 1) symptomatic treatment, using acetylcholinesterase inhibitor which increased the availability of acetylcholine (ACh) at the neuromuscular junction and 2) reduced auto-antibody binding to nicotinic acetylcholine receptors by using immunosuppressive drug, immunoglobulin, plasma exchange or thymectomy. Many studies have reported benefit of thymectomy in MG. Patient’s age, sex, presence of thymoma, severity of MG, presence of AChR antibody or MuSK antibody, and seronegative myasthenia are important factors when considering thymectomy. The previous randomized, controlled trial compared the effects
of thymectomy and prednisone therapy versus prednisone therapy alone in 126 generalized MG patients with positive AChR antibody and disease duration less than 5 years. The results supported the benefit of thymectomy in non-thymomatous MG patients. Thymectomy group had lower time-dependent averaged quantitative MG score, lower average daily dose of prednisone, lower average daily dose of azathioprine and less hospitalization for MG exacerbation. Another study from Thailand also showed that thymectomy group had higher complete remission and improvement rates.

Thymectomy has been recommended in 1) all thymoma cases, regardless of types of MG and 2) non-thymomatous generalized MG patients with positive AChR antibody. Thymectomy is recommend early after symptom onset and all thymus tissue have to be completely removed. Improvement of MG symptoms after thymectomy occurs gradually after several months, up to 3 years postoperatively. Although thymectomy is the current standard treatment, long-term outcomes including time to improvement or remission after thymectomy, the need of immunosuppressive medications, treatment complication and factor related to remission are still unclear.

The primary goal of this study was to determine the treatment outcomes in generalized MG patients with or without positive AChR antibody, which included remission rate, minimal manifestation status [as defined by the Myasthenia Gravis Foundation of America (MGFA) classification], total dose of immunosuppressive and treatment complication, in thymectomy and non-thymectomy MG patients. The secondary goal was to determine the benefit of thymectomy in non-thymomatous generalized MG patients with negative AChR antibody.

**METHODS**

We reviewed the medical records of patients who were diagnosed with MG at Neurological Institute of Thailand (NIT) during 1st January 2014 – 31st December 2018. Inclusion criteria was newly diagnosed generalized MG with minimal of 2 years follow up. The diagnosis of MG was based on the clinical presentation and the present of AChR antibody or abnormal repetitive nerve stimulation (RNS). Patients with inadequate data on treatment or follow up were excluded.

Patients were classified into two groups: 1) Patients underwent thymectomy (thymectomy group) and 2) Patients whom thymectomy was not performed (medication group). Demographic features, severity of MG, Medical Research Council (MRC) Scale, disease duration, clinical course, antibody status, investigational results, treatment, treatment response, follow-up duration, Myasthenia Gravis Foundation of America (MGFA) clinical classification at diagnosis and MGFA post-intervention status (MGFA-PIS) at the last visit were compared between those two groups.

MGFA clinical classification divided MG into 5 main subgroups (classes I-V) based on clinical features and disease severity. Detailed MGFA clinical classification was shown in Supplement 1. MGFA post-intervention status (MGFA-PIS) was used to evaluate the clinical changes in MG patients after treatment, as improvement, worsening or no difference. MGFA-PIS is shown in Supplement 2.

The primary outcome was the rate of remission and rate of minimal manifestation status according to MGFA-PIS at the last visit. The secondary outcome was the required dosage of immunosuppressive medications such as prednisone and azathioprine over the period of 2 years.

**Statistical analysis**

Descriptive summaries were presented as frequencies and percentages for categorical variables and median/mean and ranges for continuous variables. Comparisons between thymectomy group versus medication group were performed using Fisher’s exact test or Wilcoxon rank sum test, as appropriate. All of the tests were two sided, and p-value less than 0.05 were considered as statistical significance. Statistical analyses were performed using SPSS for windows version 16.0. The present study design was approved by the Institutional Review Board.

**RESULT**

**Demographic characteristics**

Seventy-six generalized MG patients were identified. The demographic and clinical characteristics is shown in Table 1. Of these, 36 (47.7%) were MG patients with thymectomy and 40 (52.3%) were MG patients with no thymectomy. There were no differences in sex, MRC score, abnormal RNS, requirement of immunosuppressive and follow up duration. Majority of the patients were female in both groups, and most of patients were younger than
60 years old. Patients in thymectomy group had younger age at evaluation (39.5 vs. 48.3 years; p = 0.010), lower MGFA class at diagnosis (p = 0.002), higher rate of positivity of AChR Ab (86.1% vs. 62.5%; p = 0.035) and more abnormality of thymus gland in CT chest (31.2% vs. 3.1%; p = 0.006).

**Response to treatment**

The follow up time in this present study was 24 months. The results are shown in Figure 1. At 6 and 12 months follow up, most patients in both groups had a good response to treatment. Most of patients had no symptoms of functional limitations from MG but had motor weakness in some muscles tested and received low-dose cholinesterase inhibitors (pyridostigmine) or some form of immunosuppressive drugs (MM-2 and MM-3, according to MGFA-PIS). At 18 and 24 months follow up, higher proportion of patients in thymectomy group was in remission than those in medication group but the results did not reach statistical significance.

*Thymectomy and acetylcholine receptor antibody*

The results are shown in Table 2 and Figure 1. At 24 months follow up, 18 patients in thymectomy group were in remission and all of them had positive AChR antibody. In contrast, none of remission patients in medication group had positive AChR antibody. MG patients with negative AChR antibody also showed some response to thymectomy. However, these are not superior than medication treatment.
Before thymectomy, both groups received similar dose of immunosuppressive drugs including prednisolone and azathioprine. However, during follow up, dosage of immunosuppressive drugs was faster reduced in thymectomy group than medication group. Regarding the dosage of medications during follow up and at 24 months follow up, patients in thymectomy group required lower dose of prednisone, azathioprine and pyridostigmine than medication group. However, the results did not reach statistical significance. The results have been shown in Figure 2.

DISCUSSION

MG is an autoimmune disease which affects neuromuscular junction. Thymectomy is recommend for thymomatous MG patients and non-thymomatous generalized MG with

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**Figure 1. Response to treatment of myasthenia gravis patients**

MM-2, The patient has received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day) for at least 1 year.

**Immunosuppressive and cholinesterase inhibitors drugs reduction**

Table 1. Response to treatment of myasthenia gravis patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MM2</th>
<th>MM3</th>
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<tbody>
<tr>
<td>Thymectomy</td>
<td>5.6%</td>
<td>94.4%</td>
</tr>
<tr>
<td>Medication</td>
<td>91.7%</td>
<td>87.5%</td>
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</table>

**At 6 months follow-up**

P = 0.303

**At 12 months follow-up**

P = 0.093

**At 18 months follow-up**

P = 0.131

**At 24 months follow-up**

P = 0.118
Figure 2. Median dose of cholinesterase inhibitors and immunosuppressive drug at first evaluation and follow up.
positive AChR antibody patients. However, benefit and long-term outcomes of thymectomy in non-thymomatous generalized MG patients with negative AChR antibody is still debated. In the present study, we observed and compared treatment response between patients who underwent thymectomy and patients who took only medications. The demographic data was similar to worldwide epidemiological study that female was predominated, and most patients were younger than 60 years old.

Both groups had a good response at 6 months follow up but complete stable remission started at 12 months follow up. Higher rate of remission was observed in thymectomy group at 18 and 24 months follow up. Other benefit of thymectomy is decreased requirement of immunosuppressive medications and pyridostigmine. Prednisolone, azathioprine and pyridostigmine were reduced faster and dosage were lower in thymectomy group than medication group similar to previous study,\textsuperscript{10} however, it did not reach statistical significance in our study. These could be explained by the fact that, in this present study, 13.9% of patients in thymectomy group had negative AChR antibody, who may gain less benefit from thymectomy. In addition, the number of patients is small therefore it was hard to show statistical significance.

The previous study showed the benefit of thymectomy in non-thymomatous generalized MG patients with positive AChR antibody but the benefit in those with negative AChR antibody is still unclear.\textsuperscript{12} The present study confirmed the benefit of thymectomy in generalized MG patient with positive AChR antibody. In thymectomy group, all patients with positive AChR antibody had complete stable remission or clinical improvement. Contrary with medication group, there is no complete stable remission in patients with positive AChR antibody and some patients were not improved at the time of last follow up. The present study also showed benefit of thymectomy in generalized MG patient with negative AChR antibody. In thymectomy group, all patient with negative AChR antibody had clinical improvement but the benefit was not equal to patient with positive AChR antibody. There was no complete stable remission in negative AChR antibody patients in thymectomy group. This benefit was explained by low-affinity antagonist IgG antibodies to AChR, as Vincent \textit{et al.} reported that, low-affinity IgG autoimmune antibodies to AChR was detected in 66% of seronegative MG patients (negative AChR and Musk antibodies).\textsuperscript{15}

Present study showed lower rate of remission (25%) when compared to the previous studies (41- 42%).\textsuperscript{7, 9} The relatively low rate of remission might be explained by several factors. Firstly, the definition of remission was different. Previous studies defined MGFA clinical classification 0 or no symptom as remission, but we used MGFA-PIS classification which remission based on no symptoms or signs of MG and patients did not taking cholinesterase inhibitors during that time. Secondly, follow up time in our study was only 2 years which may possible be too short as remission in thymectomy patients were rarely reported at 2 to 3 years and may be seen as late as 5 years after surgery.\textsuperscript{16} This relatively short follow up time after thymectomy might also be one of the reasons why the lower requirement dose did not reach statistical significance.


d\textsuperscript{13} Limitations of the present study include: 1) it was a retrospective observational study, the decision whether to proceed to thymectomy was made by the attending neurologists, 2) small number of patients therefore it was hard to show statistical significance, 3) lacking the information regarding surgical technique, complication and tissue pathology as patients were refer to other institute for thymectomy, 4) patients with thymoma who underwent thymectomy were also

<table>
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<tr>
<th></th>
<th>Thymectomy N = 36</th>
<th>Non-Thymectomy N = 40</th>
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<tr>
<td></td>
<td>AChR Ab N = 31</td>
<td>AChR Ab N = 5</td>
</tr>
<tr>
<td>Remission (%)</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>MM-2</td>
<td>9.7</td>
<td>0</td>
</tr>
<tr>
<td>MM-3</td>
<td>61.3</td>
<td>100</td>
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<tr>
<td>Improved (%)</td>
<td>0</td>
<td>8</td>
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<td>Unchanged (%)</td>
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Table 2: AChR antibody and treatment response at 24 months follow up

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included in the thymectomy group, this would influence the outcome after thymectomy when analyzing the data and compare with other studies which were done on non-thymomatous patients only.

In conclusion, the present study demonstrated that thymectomy was associated with a high probability of achieving remission and requiring lower dose of cholinesterase inhibitors and immunosuppressive drugs when compared to medication group. Therefore, thymectomy should be considered for all generalized MG patient with positive AChR antibody patient and may be considered in generalized MG with negative AChR antibody patient.

ACKNOWLEDGMENT

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DISCLOSURE

Conflict of interest: None

REFERENCES

Supplement 1 - MGFA clinical classification

Class I MG is characterized by the following:
   I. any ocular muscle weakness.
   II. may have weakness of eye closure.
   III. all other muscle strengths are normal.

Class II MG is characterized by the following:
   I. mild weakness affecting muscles other than ocular muscles,
   II. may also have ocular muscle weakness of any severity.

Class IIa MG is characterized by the following:
   I. predominantly affecting limb, axial muscles, or both
   II. may also have lesser involvement of oropharyngeal muscles.

Class IIb MG is characterized by the following:
   I. predominantly affecting oropharyngeal, respiratory muscles, or both,
   II. may also have lesser or equal involvement of limb, axial muscles, or both.

Class III MG is characterized by the following:
   I. moderate weakness affecting muscles other than ocular muscles,
   II. may also have ocular muscle weakness of any severity.

Class IIIa MG is characterized by the following:
   I. predominantly affecting limb, axial muscles, or both,
   II. may also have lesser involvement of oropharyngeal muscles.

Class IIIb MG is characterized by the following:
   I. predominantly affecting oropharyngeal, respiratory muscles, or both,
   II. may also have lesser or equal involvement of limb, axial muscles, or both.

Class IV MG is characterized by the following:
   I. severe weakness affecting muscles other than ocular muscles,
   II. may also have ocular muscle weakness of any severity.

Class IVa MG is characterized by the following:
   I. predominantly affecting limb, axial muscles, or both,
   II. may also have lesser involvement of oropharyngeal muscles.

Class IVb MG is characterized by the following:
   I. predominantly affecting oropharyngeal, respiratory muscles or both,
   II. may also have lesser or equal involvement of limb, axial muscles, or both.

Class V MG is characterized by the following:
   I. intubation with or without mechanical ventilation, except when employed during routine postoperative management,
   II. the use of feeding tube without intubation places the patient in class IVb.
Supplement 2 - MGFA Post-intervention Status (MGFA-PIS)

Complete Stable Remission (CSR) - The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.

Pharmacologic Remission (PR) - The same criteria as for CSR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.

Minimal Manifestations (MM) - The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.

  MM-0 - The patient has received no MG treatment for at least 1 year.
  MM-1 - The patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy.
  MM-2 - The patient has received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day) for at least 1 year.
  MM-3 - The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.

Change in Status

Improved (I) - A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.

Unchanged (U) - No substantial change in pretreatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.

Worse (W) - A substantial increase in pretreatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score.

Exacerbation (E) - Patients who have fulfilled criteria of CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria.

Died of MG (D of MG) - Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy.