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Case Series – General Neurology

Case Series: Clinical Impact of Plasmapheresis and Thymectomy on Early-Onset Myasthenia Gravis

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Keywords
Myasthenia gravis · Thymectomy · Plasmapheresis · Autoimmune disorder

Abstract
Thymectomy is a common procedure performed in cases of myasthenia gravis (MG) with a thymoma or general MG that does not improve with medical therapy. This procedure is usually preceded by plasmapheresis to prevent the occurrence of myasthenic crisis and improve clinical outcome after thymectomy. Early-onset MG has a different phenotype than late-onset MG. So far, the effectiveness of plasmapheresis followed by thymectomy in early-onset MG remains unclear because of the conflicting results of previous studies. We present 5 early-onset MG patients who underwent plasmapheresis followed by thymectomy in the 2007–2020 period. Follow-up was done 1 year after thymectomy. We describe clinical features and postoperative data and evaluate the clinical outcome after thymectomy. Muscle strength was assessed by the Medical Research Council scale. Evaluation of clinical stage before and after thymectomy were carried out with the modified Osserman classification. All patients showed improvement (100%) in the clinical grade of the modified Osserman classification: 3 patients were in the

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complete remission category and 2 patients were in the improved category. All patients with general weakness experienced improvement in muscle strength at the 1-year evaluation.

Introduction

Myasthenia gravis (MG) is an autoimmune disorder affecting the neuromuscular junction that has characteristic symptoms of fluctuating weakness involving ocular, bulbar, extremity, and respiratory muscles in various combinations [1]. The incidence of MG is estimated to reach 2–5 per 100,000 people per year [2], with age of onset generally above 50 years in men and between the ages of 20 and 30 years in women [1, 2].

The thymus gland has been proposed to have a role in MG through production of acetylcholine receptor antibody (AChR), particularly in patients with thymic hyperplasia or thymoma [1, 3]. In addition, thymoma is also one of the main risk factors for the formation of titin and RyR antibodies, which are associated with more severe clinical symptoms of MG [3]. Thymectomy is a gold standard procedure for MG with thymoma or hyperplasia of the thymus and in nonthymomatous MG patients who do not respond to medication [1, 3]. The study by Wolfe et al. [4] showed that MG exacerbation rates were lower in patients undergoing thymectomy than in patients treated only with prednisone (9 vs. 37%).

Plasmapheresis is another mainstay therapy for MG [1, 5]. Research conducted by Nagayasu et al. [5] showed that the rate of post-thymectomy pharmacological remission in the group undergoing plasmapheresis reached 79% compared to 50% in the group not undergoing plasmapheresis ($p = 0.0427$). Although effective in relieving symptoms, the effects of plasmapheresis are temporary due to the ongoing process of antibody resynthesis [6]. The use of plasmapheresis is also hindered due to possible side effects (hypotension, coagulopathy, etc.) and the high costs [7]. The role of plasmapheresis in improving outcome of thymectomy is still controversial.

Based on the age of the patient when symptoms first appeared, MG was classified as early onset if the age of onset is below 50 years and late onset for more or equal to 50 years [8]. Neuromuscular symptoms in early-onset MG tend to be less severe and less associated with thymoma compared to late-onset MG [3, 8]. The presence of antibodies to striated muscle antigens, especially titin antibodies that are commonly found in thymoma and late-onset MG, are the main immunologic differences between early- and late-onset MG [9].

So far, effectiveness of plasmapheresis and thymectomy in improving the outcome of thymectomy in early-onset MG remains unclear. Early-onset MG is associated with a higher frequency of AChRs compared to late-onset MG (73.3 vs. 65%) [10]; thus, theoretically, plasmapheresis should provide a better response to early-onset MG, but the study conducted by Usmani et al. [11] showed different results: only 30% of patients with early-onset MG achieved complete remission, which was lower than 68% in late-onset patients. In this case series, we evaluated clinical improvement for a year in patients with early-onset MG who underwent plasmapheresis followed by thymectomy at Siloam Lippo Village Karawaci Hospital.

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Clinical characteristics details of patients are shown in Table 1. Out of the total 5 patients, 3 were male and 2 were female. The average age at onset was 37.8 years with an age distribution of 16–49 years. One patient (20%) had pure ocular symptoms, while the other 4 (80%) experienced symptoms of general weakness. Based on the modified Osserman classification, 1 patient (20%) was included in stage I, 2 patients (40%) in stage II, and 2 patients (40%) in stage III. The average duration of symptomatic symptoms before the thymectomy was 6.2 months with a minimum duration of 1 month and a maximum duration of 12 months. All patients received preoperative therapy with acetylcholinesterase inhibitors (pyridostigmine) and plasmapheresis, while 2 patients received additional corticosteroid therapy (40%).

Details of the operative and postoperative data are shown in Table 2. All patients were successfully extubated after surgery. The average duration of surgery, postoperative intubation, ICU room care, and hospitalization were 1.7, 8.9, and 33.6 h, and 12 days, respectively. Postoperative complications found were 1 case of surgical wound infection (20%) and 1 case of pleural effusion (20%). There were no cases of postoperative myasthenic crisis. The results of thymic pathology examination showed 2 cases of thymoma (40%), 1 case of thymic hyperplasia (20%), and 2 cases of thymic involution (20%).

Follow-up was done 1 year after thymectomy. The results of the follow-up showed that all patients responded positively, with 3 patients achieving complete remission status (60%), while 2 patients were in the improved category (40%). All patients with general weakness (n = 4) showed improvement in muscle strength. At 1-year follow-up, 3 patients showed an MRC muscle strength scale of 5, and 1 patient showed an MRC muscle strength scale of 4. There were no recurring episodes or cases of mortality during follow-up.

We describe 2 cases of early-onset MG (cases I and IV) who had undergone plasmapheresis followed by thymectomy with the same preoperative severity (Osserman stage III), but with different thymic pathology.

Case I

A 16-year-old boy presented with complaints of weakness in all 4 limbs accompanied by difficulty swallowing for 5 days. Bilateral ptosis was found on physical examination. Muscle strength scale was 3 in all extremities. The patient was diagnosed with MG based on clinical symptoms and rapid nerve stimulation examination, which showed a decremental decrease of >10% in the abductor muscles of the minimi digiti, trapezius, and right ocular orbicularis. The results of a chest CT scan (Fig. 1) showed no signs of malignancy in the thymoma. The patient was treated with pyridostigmine, methylprednisolone, and plasmapheresis. During the 15 days of treatment, the patient did not show significant improvement, so thymectomy was performed. Histological examination confirmed thymus involution. The patient showed post-thymectomy improvement and was maintained with pyridostigmine therapy. At the 1-year evaluation, the patient showed improvement in symptoms (from the modified clinical stage of Osserman III to II, and on the MRC scale from 3 to 4).

Case IV

A 49-year-old man presented with the main complaint of weakness of the entire limbs for 2 years. The patient also complained of difficulty in speaking and slurred speech when talking for a sufficient time. On physical examination, there was right ptosis. Muscle strength based on the MRC scale was 3. The patient was treated with pyridostigmine and methylprednisolone. Chest CT scan (Fig. 2) showed a mass in the thymus area suggestive of thymoma. Thymectomy was performed after plasmapheresis, with histological results showing a thymoma. During treatment, the patient's condition tended to be stable and the patient was discharged after 12 days of treatment. In the evaluation 1 year after thymectomy, the patient did not complain of any symptoms (asymptomatic), but he still consumed the acetylcholinesterase inhibitor. No significant abnormalities were found on physical examination.

Discussion

Here, we present 5 early-onset MG patients undergoing plasmapheresis and thymectomy. The patients' age of onset ranged from 16 to 49 years, with 3 male patients and 2 female patients. Duration of follow-up was 1 year after thymectomy. Out of a total of 5 patients, all (100%) patients had a positive response after thymectomy, with details of 3 patients fulfilling complete remission criteria, while 2 patients were in the improved category. Evaluation of muscle strength based on the MRC scale showed improvement in all MG patients with general weakness. These results are in accordance with previous studies conducted by Budde et al. [12], which showed that early-onset MG was associated with more significant improvement in clinical outcomes than late-onset MG (81 vs. 55%). The study also showed that the age of 50 years was a cutoff value in accordance with the multivariate model [12]. Similar results were found by Nagayasu et al. [5] where 79% of patients who underwent plasmapheresis experienced complete remission. The clinical improvement rate in this study is higher than that of Nagayasu et al. [5] (100 vs. 79%), presumably because all of our study cases were early-onset MG, since previous studies found that clinical outcome improvement was more significant in early-onset than in late-onset MG [12].

The average durations of surgery, postoperative intubation, ICU ward, and inpatient treatment were 1.7, 8.9, and 33.6 h, and 12 days, respectively. These results are largely different from the results of previous studies. Saeteng et al. [13] reported that the average duration of surgery was 1.68 h, the duration of postoperative intubation was 29 h, the duration of treatment in the ICU was 55.2 h, and the duration of hospitalization was 6 days. In contrast, El-Bawab et al. [6] reported that the average durations of intubation, ICU care, and length of stay were 5.3 and 45.6 h, and 9.2 days, respectively. The difference in average duration is probably due to differences in postoperative care protocols and ICU room care in each institution. The long duration of hospitalization in our study was due to plasmapheresis generally carried out on days 3–4 of treatment.

The rate of postoperative complications in this study was 40% (2 out of 5); 1 patient had a surgical wound infection and 1 patient had pleural effusion. This result is higher than the results of previous studies. Saeteng et al. [13] reported a post-thymectomy complication rate

of 3.5% (3 out of 86), with 1 case each of infection, bleeding, and myasthenic crisis occurring. The reported complication rate for Mozaffar et al. [7] was 24% (11 of 46), with details of 4 patients experiencing atelectasis, 5 patients with myasthenic crisis, 1 patient with respiratory distress, and 1 patient with urinary tract infection. The high complication rate in this study is due to the smaller number of samples compared to previous studies.

Based on previous research, after thymectomy it generally takes 26 months to achieve improvement [14]. Different results were found in the cases we presented, where all cases with a follow-up duration of less than 26 months showed improvement based on the modified Osserman classification. Of the 2 cases of MG with thymoma, all (100%) showed positive response after thymectomy; one patient had improvement and the other had a complete remission. These results differ from previous studies which showed that thymoma tends to be associated with a poor prognosis after thymectomy [15].

Our research limitation is the study design in the form of a case series because of the small number of research subjects, so there is a possibility that myasthenic crisis and other complications did not occur due to chance. We also did not make a comparison between early-onset and late-onset MG, nor a comparison of clinical evaluations in patients undergoing pre-thymectomy plasmapheresis and in patients who only had thymectomy. We did not perform AChR and other MG antibodies tests in all patients due to cost limitations and limited facilities in our country.

Conclusion

Plasmapheresis followed by thymectomy in early-onset MG showed significant clinical outcome improvement, where 3 out of 5 cases achieved complete remission and 2 cases were in the improved category. All patients with general weakness experienced improvement in muscle strength at the 1-year evaluation.

Statement of Ethics

The authors have no ethical conflicts to disclose. The patients described in this article have given their written informed consent to publish their case (including publication of images).

Conflict of Interest Statement

All authors declare no conflicts of interest.

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Author Contributions

This study was designed, directed, and coordinated by Y.M.T.S. as the principal investigator who provided conceptual and technical guidance for all aspects of the project. R.J.K., A.P., and V.H. contributed equally to manuscript conceptualization, writing, editing, and review for submission.

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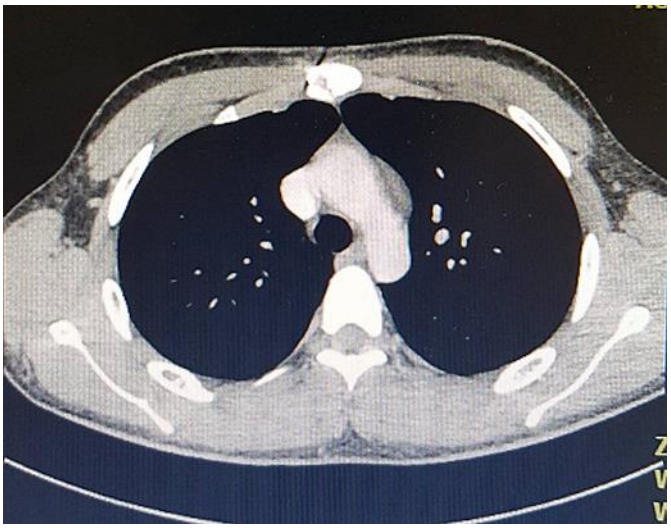

Fig. 1. The results of a chest CT scan in case I showed normal thymic morphology.

Fig. 2. The results of a chest CT scan in case IV showed a visible heterogeneous mass with contrast enhancement in the anterior mediastinum suggestive of a thymoma.

Table 1. Clinical characteristics and evaluation 1 year after thymectomy

Patient	Age of onset, years	Gender	Symptom	Duration, months	Pre-operative modified Osserman	Pre-operative muscle strength	Thymic pathology	Preoperative management	Post-operative modified Osserman	Post-operative muscle strength	Evaluation
Case I	16	Male	General weakness	1	III	3	Involution	Acetylcholinesterase inhibitor, methylprednisolone, plasmapheresis	II	4	Improved
Case II	39	Female	Ocular weakness	4	I	5	Hyperplasia	Acetylcholinesterase inhibitor, plasmapheresis	Asymptomatic	5	Complete remission
Case III	44	Female	General weakness	12	II	4	Involution	Acetylcholinesterase inhibitor, plasmapheresis	Asymptomatic	5	Complete remission
Case IV	49	Male	General weakness	2	III	3	Thymoma	Acetylcholinesterase inhibitor, methylprednisolone, plasmapheresis	Asymptomatic	5	Complete remission
Case V	41	Male	General weakness	12	II	4	Thymoma	Acetylcholinesterase inhibitor, plasmapheresis	I	5	Improved

Table 2. Postoperative and operative data

Patient	Operation duration, h	Postoperative intubation duration, h	ICU care duration, h	Hospital stay, days	Complication
Patient I	2	16.5	48	15	–
Patient II	2.5	6.5	36	13	Wound infection
Patient III	1	4.5	24	15	–
Patient IV	1	7	36	11	–
Patient V	2	10	24	6	Pleural effusion