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Effect of thymectomy for thymic atrophy in myasthenia gravis: A retrospective study on 93 patients

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ABSTRACT

To clarify the efficacy of thymectomy among myasthenia gravis (MG) patients with and without thymoma. We classified MG patients who underwent thymectomy into 3 groups, such as thymic atrophy group, thymic follicular hyperplasia (TFH) group and thymoma group. We compared the data of clinical features and postoperative prognosis at very short-term, short-term, and medium-term. The clinical course of MG patients with atrophic thymus after thymectomy was even better than those of TFH or thymoma, in this retrospective study. However, we found no significant differences in the comparison of mean dose of prednisolone between the 3 groups at each time point.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction characterized by muscle weakness, production of antibodies against skeletal muscle acetylcholine receptors (AChRAb), and frequent clinical response to therapeutic thymectomy (Gilhus and Verschuuren, 2015). Thymomatous MG is the clinical setting in which therapeutic thymectomy is routinely performed. However, it remains unproven whether thymectomy is effective or not in non-thymomatous MG, especially in cases of thymic atrophy. Although a randomized controlled trial (the MGTX study) reported the impact of thymectomy on myasthenic symptoms in patients with non-thymomatous MG (Wolfe et al., 2016), we should elucidate the relationship between the efficacy of thymectomy, thymus pathology, and the treatment requirements. To clarify the association with thymus pathology and the postoperative prognosis, we conducted a retrospective study on patients diagnosed with MG in a decade. We classified MG patients into 3 groups, such as thymic atrophy group, thymic follicular hyperplasia (TFH) group and thymoma group, based on the pathological findings. We evaluated clinical characteristics, as well as treatments and prognosis among the 3 groups.

2. Materials and methods

2.1. Subjects

We retrospectively reviewed the clinical records of 178 patients (male: 56, female: 122; average age: 53.9 ± 20.6) with confirmed MG, who attended Kumamoto University Hospital, between April 2005 and September 2015. Diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) with amelioration of symptoms after intravenous administration of anticholinesterase, decremental muscle response to a train of low-frequency repetitive nerve stimuli, or the presence of AChRAb. To avoid potential bias, we enrolled patients in various stages of illness in this single center cross-sectional study. Of these patients with MG, 96 patients with thymomatous MG or generalized non-thymomatous MG underwent thymectomy using the median sternotomy approach, until January 2007, after when we adopted the video-assisted thoracoscopic surgery approach, and identified thymic pathology (Mori et al., 2007; Yoshioka et al., 2006). As this study was based on detailed information for the entire course of treatment, 3 patients were excluded for insufficient data. Finally, 93 MG patients were analyzed.

Serum AChRAb titers were determined by a radioimmunoassay using ^{125}I-a-bungarotoxin, and levels of 0.3 nmol/L were regarded as positive. Muscle-specific tyrosine kinase antibodies positive MG and seronegative MG patients were excluded from this study.

The following basic patient information was collected: gender; age; age at onset; disease duration; MG Foundation of America (MGFA)

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classification (Jaretzki et al., 2000); and AChRAb status. MGFA classification was based on Chest CT scans were performed for diagnosis of MG to screen for thymomas. The degree of TFH of the thymus was classified into 5 grades according to the classification of the MG study group of the Ministry of Health and Welfare of Japan in 1977: grade 0, involuted thymus; grade I, accumulation of lymphocytes in the distended medulla; grade II, 1 follicle in 1 section; grade III, 2 to 4 follicles in 1 section; and grade IV, >5 follicles in 1 section or >1 follicle in each lobule. We defined grade 0 or grade I as thymic atrophy, and grade II or above as TFH in non-thymomatous MG. Treatment-related information included: MGFA post-intervention (PI) status (Jaretzki et al., 2000); age at thymectomy; thymic histology; current prednisolone (PSL) dose; course of PSL dose; use of calcineurin inhibitors (CNIs); use of pyridostigmine; steroid pulse therapy; plasmapheresis (PP); and intravenous immunoglobulin (IVIg). Histological analyses of the thymus were performed after thymectomy. In the present study, diagnoses of thymic atrophy, TFH and thymoma were made by pathologists, certified by the Japanese Society of Pathology, in our institute (Kondo and Monden, 2005).

We classified the MG patients who underwent thymectomy into 3 groups, such as thymic atrophy group, TFH group and thymoma group, based on pathological findings. We compared the data of clinical features and thymectomy outcomes among pre-thymectomy, 1 month, 1 year, and 3 years after thymectomy.

2.2. Statistics

Commercially available statistical software was used for data analysis (SigmaPlot®). Data that were normally distributed were analyzed by one-way ANOVA. Pairwise comparisons were evaluated by Student-Newman-Keuls methods. For data that was not normally distributed, one-way ANOVA was used to provide ranking. Comparisons with $p < 0.05$ were considered to be significantly different. We undertook statistical analysis of MGFA PI status at 1 year and 3 years only, because, for example, "CSR" is defined as the status of the patients has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. However, we consciously evaluated MGFA PI status at 1 month to illustrate the trend of postoperative clinical course in a comprehensible way.

3. Results

Of 93 MG patients (27 males and 66 females; 56 ± 17 years old) who underwent thymectomy, patients with thymic atrophy were 25 (27%), patients with TFH were 29 (31%), and patients with thymoma were 39 (42%). Clinical features at the baseline of patients with MG and operative procedure are summarized in Table 1. In the TFH group, age, age at onset and age at thymectomy are significantly lower, and serum AChRAb titers were significantly higher than the other 2 groups. Moreover, the number of late onset MG cases was significantly fewer in the TFH group, compared to the thymic atrophy group and thymoma group (Uzawa et al., 2015). The results of the chest CT scan in each group were as follows; in the group of thymic atrophy, thymic atrophy was identified in 22 patients (88%) and residual thymus was identified in 3 patients (12%). In the TFH group, thymic atrophy was identified in 9 patients (33%), residual thymus was identified in 14 patients (52%) and swelling of thymus was identified in 4 patients (15%) (we could not confirm CT scans in 2 patients). Moreover, in the thymoma group, thymoma was identified in 34 patients (97%) and nodule was identified in 1 patient (3%), after excluding 5 patients that we could not confirm CT scans. Administration of IVIg was more frequent in thymoma group, during the entire course, in the intervention for exacerbation of MG (Table 2).

We demonstrated MGFA PI status, at 1 year and 3 years after thymectomy, and divided each group into "red" subgroup (i.e. CSR, PR, and MM), "white" subgroup (i.e. I) and "blue" subgroup (i.e. U, and W) according to MGFA PI status (Fig. 1). The thymic atrophy group, TFH group, and thymoma group significantly improved over time ($p < 0.001$, respectively, Fig. 1). And, significant differences were found among the 3 groups at the time points of 1 year and 3 years after thymectomy ($p = 0.002$, and <0.001, respectively, Fig. 1). "Red" subgroup in each group, especially in the thymic atrophy group has increased yearly in the postoperative clinical course. In regard to serum AChRAb, in the TFH group, mean titer was significantly higher than in the other 2 groups at the baseline, and it decreased with significant difference at the time point of first postoperative month, compared to the thymic atrophy group and thymoma group ($p = 0.022$, 0.053, and 0.123, respectively, Fig. 2). In those days, we gradually increased oral PSL for patients with MG, but we found no significant differences in the comparison of mean dose of oral PSL among the 3 groups at each time point of postoperative state ($p = 0.287$, 0.576, and 0.705, respectively, Fig. 3). No statistical significance was also detected in mean dose of CNIs among the 3 groups at each time point.

Table 1
Clinical features of patients with MG at pre-thymectomy and operative procedure.

		Thymic atrophy group	Thymic follicular hyperplasia group	Thymoma group	*p*-Value
Number of patients		25	29	39	
Age (yr)		64.1 ± 13.6	43.8 ± 18.0	59.9 ± 12.3	<0.001
Age at onset (yr)		59.5 ± 13.4	37.8 ± 17.2	54.6 ± 12.6	<0.001
Late onset MG (%)		20 (80)	6 (21)	29 (76)	<0.001
Age at thymectomy (yr)		60.8 ± 12.7	39.1 ± 17.0	55.3 ± 12.3	<0.001
Sex, female (%)		14 (56)	24 (83)	28 (72)	0.163
MGFA classification	I (%)	0 (0)	2 (7)	7 (18)	0.339
	II (%)	24 (96)	23 (80)	26 (67)	
	III (%)	0 (0)	3 (10)	3 (8)	
	IV (%)	0 (0)	0 (0)	0 (0)	
	V (%)	1 (4)	1 (3)	1 (2)	
	Unclassified (%)	0 (0)	0 (0)	2 (5)	
Anti-AChR Ab (nmol/L)		27.9 ± 28.7	354.3 ± 1084.6	51.2 ± 69.4	0.015
PSL (mg)		1.2 ± 6.0	3.7 ± 9.6	5.1 ± 11.7	0.198
Tacrolimus (mg)		0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.5	0.494
Cyclosporin A (mg)		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	1.000
VATS for thymectomy (%)		16 (64)	18 (62)	10 (26)	0.002

MG = myasthenia gravis; MGFA = MG foundation of America; anti-AChRAb = anti-acetylcholine receptor antibodies; PSL = prednisolone; VATS = video-assisted thoracoscopic surgery.

4. Discussion

The MGTX trial could elucidate the efficacy of thymectomy in patients with non-thymomatous MG (Wolfe et al., 2016; Aban et al., 2008; Newsom-Davis et al., 2008; Marx et al., 2012). In the present study, we explored outcome of MG, changes of AChRAb titers, and medication usage in depth, based on thymic histology. We demonstrated that all 3 groups demonstrated an improved long-term outcome by thymectomy, even thymic atrophy group. "Red" subgroup including CSR, PR, and MM in MGFA PI status existed in each group, especially in the thymic atrophy group. We found statistical differences in MGFA PI status between the 3 groups at the time points of 1 year and 3 years. However, no significant differences in mean dose of PSL and CNIs were detected among the 3 groups at each time point. Administration of IVIg was more frequent in the thymoma group, because patients with thymomatous MG experienced more frequent episodes of exacerbations than patients with non-thymomatous MG. Although thymectomy has been generally accepted as the most viable option of treatment for MG with thymoma or TFH, we concluded that the efficacy of the