Clinical Study

Headache Associated with Myasthenia Gravis: The Impact of Mild Ocular Symptoms

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Myasthenia gravis (MG) patients visiting outpatient clinics frequently complain of headache. However, there have been few reports on the relation between chronic headache and myasthenia gravis (MG). We aimed to investigate whether MG symptoms affect the development or worsening of chronic headache. Among the 184 MG patients who were followed at the MG clinics, tension-type headache was observed in 71 (38.6%) patients and 9 (4.9%) complained of migraine. Twenty-five (13.6%) complained that headache appeared or was exacerbated after the MG onset. The investigation into differences in the clinical characteristics of the MG patients showed that women tended to suffer from MG-associated headache more often than men. Logistic regression analyses revealed that female gender and mild ocular symptoms were independently predictive of headache associated with MG. Our results suggest that treatment of chronic headache should be required to improve the quality of life in MG patients.

1. Introduction

Headache is one of the most common neurological symptoms. At our clinics, we have found that some myasthenia gravis (MG) patients complain of headache more than the known MG-related symptoms. In these cases, the headaches could have a more negative impact on the quality of daily life than the other MG manifestations. It seemed that certain MG symptoms induce the development or worsening of headache, but there have been only a few case reports concerning headache in MG patients [1, 2]. On the other hand, some major neurological diseases, including Parkinson's disease [3, 4] and multiple sclerosis [5, 6], have been reported to be associated with headache. In this paper, to investigate the relationship between headache and MG, we examined whether each of the MG symptoms could be a cause of headache in MG patients.

2. Methods

2.1. Patient Selection and Diagnosis of Headaches. We studied 184 patients with MG (60 men and 124 women; mean $\pm$ SD

age, 55.9 ± 17.0), who were followed at the MG clinics of 2 institutions, Keio University Hospital and Hanamaki General Hospital in Japan, from November 2007 to April 2008 and had been followed up for at least 1 year. The diagnosis of MG was made based on the following criteria: typical history and signs of fluctuating weakness of voluntary muscles, presence of serum antiacetylcholine receptor antibodies (AChR Ab), definite clinical improvement on injection of the cholinesterase inhibitor, edrophonium, and decremental pattern on repetitive nerve stimulation [7]. The mean $\pm$ SD onset age and duration after onset in the 184 patients were 45.9 ± 18.0 years old and 8.4 ± 8.1 years, respectively. First, among MG patients, we diagnosed primary headaches according to the International Classification of Headache Disorders: 2nd edition (ICHD-II), based on physical and neurological examinations and head CT and/or MRI. Secondly, we examined the MG symptoms and characteristics of their headaches in detail in addition to using the questionnaire as a reference.

2.2. Division of the QMG Score. To evaluate which symptoms of MG appeared when their headache occurred, MG

symptoms at the outpatient clinic were graded according to a quantitative MG scoring system (QMG score) consisting of 13 items [8]. As Bhanushali et al. separated three of the QMG score items as a discrete ocular component (ocular-QMG score) in order to monitor the severity of ocular symptoms independently, we divided the test items of the QMG score into four subgroups according to their proximity in the body [9]. That is, we defined double vision on lateral gaze, ptosis, and facial muscle weakness as “ocular symptoms,” swallowing and dysarthria after counting aloud from 1 to 50 as “bulbar symptoms,” outstretching of either an arm or leg, or gripping of either hand as “limb symptoms,” and vital capacity % predicted and head lifting as “trunk symptoms.” All data and clinical information were obtained after the patients had given their informed consent, and the study was approved by the institutional review board of each hospital.

2.3. Statistical Analyses. Statistical assessments in this study, including Student's *t*-test, chi-square test, and logistic regression analyses, were performed using a statistical software program (StatView 5.0; SAS Institute Inc., Cary, NC). Values of $P < 0.05$ were considered to indicate statistical significance.

3. Results

3.1. Analysis of Headache in MG Patients. First, with respect to primary headache, 71 of the 184 MG patients (38.6%) were diagnosed with tension-type headache, and 4.9% (9/184) were diagnosed with migraine based on the ICHD-II [10]. Next, in our examination of the relationship between the onset of MG and headache, 13.6% (25/184) of the MG patients experienced headache associated with MG which appeared or was exacerbated after they were diagnosed with MG. Headache worsened in 15 patients, and headache initially appeared in 10 patients after MG onset.

The characteristics of MG-associated headache are shown in Figure 1. In regard to frequency, 48% (12/25) of the patients with MG-associated headache complained of headache 1–3 times a month. 20% (5/25) had headache every day. 16% had headache only irregularly over a certain period. 12% of patients had headache 1–4 times per week, with one patient complaining of severe pain more than twice a day (Figure 1(a)). The results in regard to the sites of headache associated with MG showed that deep in the orbit and back of the neck were the most favorite sites seen in 84% (21/25) and 60% (15/25) of the patients with MG-associated headache, respectively. Headache also often occurred in the temporal portion (32%), one side of the head (32%), the frontal portion (28%) or the whole head (20%). The surroundings of the orbit (12%), the face (12%), and the parietal portion (8%) were rarely documented as the sites of headache associated with MG (Figure 1(b)).

We also evaluated which symptoms of MG developed during the period of headache. Head dropping (68%) and ptosis (60%) were most frequently observed. General fatigue (56%) and double vision (52%) also often occurred, and limb weakness, chewing difficulty, shortness of breath, and

talking difficulty were complications in 24%, 16%, 12%, and 8% of patients, respectively.

Then, we investigated the demographic and clinical features of MG patients who experienced appearance or exacerbation of headache after MG onset and those who did not (Table 1). MG symptoms at the outpatient clinic were evaluated according to the quantitative MG scoring system (QMG score) [8]. As Bhanushali et al. described previously [9], we divided the test items of the QMG score into 4 subgroups, where double vision on lateral gaze, ptosis, and facial muscle weakness belonged to the subgroup of “ocular symptoms.” The results suggested that there were markedly significant differences in female gender ($P = 0.03$) between the two groups, whereas there were no differences in mean age, follow-up period, seropositivity of autoantibodies to the acetylcholine receptor, presence of thymoma, or history of treatments, including thymectomy and administration of prednisolone and calcineurin inhibitor (Table 1). Notably, there were also no significant differences in occurrence or aggravation of headache according to the severity of QMG score.

3.2. Clinical Factors Associated with Aggravation of Headache in MG Patients. Finally, we examined which types of clinical factors affected headache in the MG patients by univariate logistic regression analysis. To consider the possibility of an association between the severity of MG and headache, each of the four types of symptoms, that is, ocular, bulbar, limb, and trunk, was separated into mild and moderate subgroups based on the mean score. The clinical factors for which the probability values were less than 0.05 in the univariate regression analysis, which were age (1.0 and 0.04 for the odds ratio and *P* value, resp.), female gender (4.3 and 0.02), age at onset (0.98 and 0.04), mild ocular symptoms (4.8 and 0.002), mild bulbar symptoms (3.1 and 0.04), and total QMG score (1.1 and 0.04), were further entered into the multivariate logistic regression analysis for determination of the independent clinical factors affecting headache associated with MG (Table 2). Multivariate logistic regression analysis revealed that female gender (4.5 and 0.02 for the odds ratio and *P*-value, resp.) and mild ocular symptoms with QMG 1–3 in the ocular score (7.2 and 0.0005) were independent clinical factors linked with headache associated with MG.

4. Discussion

This study disclosed that 38.6% of the MG patients had tension-type headache and 4.9% had migraine according to the ICHD-II [10]. Additionally, it was notable that 13.6% of the MG patients experienced headache associated with MG. In regard to the general characteristics of MG patients, headache was affected by female gender but not by the age, the disease duration, or the severity of symptoms. Moreover, the logistic regression analysis suggested that both female gender and mild ocular symptoms might have influence on headache associated with MG.

Mild ocular symptoms indicate a slight degree of diplopia or ptosis in MG patients, which fluctuates dynamically and might lead to worsening of headache. In contrast, the MG

TABLE 1: Demographic and clinical features of patients with MG-associated headache.

	MG-associated headache (+) (<i>n</i> = 25)	MG-associated headache (−) (<i>n</i> = 159)	<i>P</i> value
Female gender	22 (88%)	102 (64%)	*0.03
Mean age, <i>y</i> (range)	49.4 ± 17.2	57.0 ± 16.8	n.s.
Mean disease duration, <i>y</i> (range)	9.2 ± 7.6	8.2 ± 8.2	n.s.
AChR-Ab positive	16 (64%)	118 (74%)	n.s.
Thymoma present	2 (8%)	37 (23%)	n.s.
Thymectomy	9 (36%)	74 (47%)	n.s.
PSL administration	15 (60%)	84 (53%)	n.s.
CNI administration	8 (32%)	43 (27%)	n.s.
QMG scores			
Total	8.4 ± 4.9	6.2 ± 4.6	n.s.
Ocular symptoms	2.2 ± 1.6	1.6 ± 1.8	n.s.
Bulbar symptoms	0.3 ± 0.5	0.2 ± 0.6	n.s.
Limb symptoms	4.9 ± 3.0	3.7 ± 2.8	n.s.
Trunk symptoms	1.1 ± 0.7	0.8 ± 0.8	n.s.

**P*-value < 0.05.

MG: myasthenia gravis; QMG: quantitative myasthenia gravis scoring; n.s.: not significant; AChR-Ab, autoantibodies to the acetylcholine receptor; PSL: prednisolone; CNI: calcineurin inhibitor.

FIGURE 1: The characteristics of MG-associated headache. (a) The frequency of headache associated with MG (*N* = 25). (b) The rates of the patients, who complained of MG-associated headache in each site. Note that headache associated with MG occurs deeply in the orbit most frequently.

patients with severe QMG scores (scores greater than 3) would have fixed symptoms with little change, which would less frequently lead to headache associated with MG. These facts suggest that fluctuation of the MG ocular symptoms could actually underlie the headache of patients with MG. When we must classify MG-associated headache based on the ICHD-II [10], it should be most similar to secondary headache as shown in the code 11.3.3 “Headache attributed to heterophoria or heterotropia.” However, MG *per se* is not included as one of the causative factors of secondary headaches in the ICHD-II.

MG is an autoimmune disease of the neuromuscular junction and does not affect the central pain pathway or other sensory tracts. We speculate that there is no direct pathologic relation between MG and headache. Indeed, since anticholinesterase agents had a partial or no effect on headache associated with MG, NSAIDs were eventually required to alleviate the pain in many cases. Based on these results, together with the results of analyses on the characteristics of MG-associated headache (Figure 1), it is difficult to distinguish MG-associated headache from tension-type headache. It was noteworthy that most of MG-associated

TABLE 2: Influences of clinical factors on headache associated with MG.

Variable	Odds ratio (95% CI)	P-value
Age (years)	1.0 (0.9–1.0)	n.s.
Female gender	4.5 (1.2–16.8)	*0.02
Age at onset (years)	1.0 (1.0–1.1)	n.s.
Mild ocular symptoms (QMG 1-3)	7.2 (2.4–21.8)	*0.0005
Mild bulbar symptoms (QMG 1-3)	2.3 (0.4–14.6)	n.s.
Total QMG score	1.1 (0.9–1.3)	n.s.

*P-value < 0.05.

MG: myasthenia gravis; n.s.: not significant; QMG: quantitative myasthenia gravis scoring; CI: confidence interval.

headache could be diagnosed with tension-type headache on the ICHD-II even when the suffered portion in 32% of the patients with MG-associated headache was restricted unilaterally (Figure 1(b)). Head dropping and fluctuation of ptosis and diplopia would accelerate visual fatigue and/or stiffness of the neck, which could be the most important precipitating factors of headache associated with MG.

It should be mentioned that this cross-sectional study has potential limitations related to recall bias and selection bias. A recall bias may have been present because patients with more severe MG symptoms may not have paid as much attention to their headache, and thus patients with mild ocular symptoms might have complained of headache more frequently. It would be another recall bias that the duration after onset of MG was as long as 8.4 years. Questionnaire asking the change of their headache characteristics between before and after the onset point had the most important role in providing the information for this study, but the duration might have been too long for completely accurate data. On the other hand, a selection bias may have played a role because the subjects of this study were limited to Japanese MG patients, who were receiving regular outpatient treatments. Due to this potential selection, neither MG patients with extremely mild symptoms nor critically severe conditions might have been included in this study. We cannot exclude these biased factors, and further investigations with a greater number of patients in all grades of MG symptoms will be needed.

In conclusion, headaches could disturb the quality of life of MG patients greatly even when their general symptoms of MG are comparatively well controlled. Careful attention to appearance or aggravation of headache in MG patients is important to improve their quality of life, especially in women with mild ocular symptoms.

Conflict of Interests

The authors declare that they have no competing interests.

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