

Clinical Analysis of Blepharospasm and Apraxia of Eyelid Opening in Patients with Parkinsonism

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Background and Purpose: Blepharospasm (BSP) and apraxia of eyelid opening (AEO) have been reported as dystonia related with parkinsonism. However, systematic analysis of clinical characteristics of BSP and AEO in parkinsonism has been seldom reported. To investigate the clinical characteristics of BSP and AEO in parkinsonism and to find out the clinical significance to differentiate parkinsonism.

Methods: We enrolled 35 patients who had BSP with or without AEO out of 1113 patients with parkinsonism (913 IPD, idiopathic Parkinson's disease; 190 MSA, multiple system atrophy, 134 MSA-p, 56 MSA-c and 10 PSP, progressive supranuclear palsy). We subdivided MSA into MSA-p (predominantly parkinsonism) and MSA-c (predominantly cerebellar) according to the diagnostic criteria proposed by Quinn. We analyzed the clinical features of BSP and parkinsonism including onset age, onset interval to BSP, characteristics of BSP, presence of AEO, coexisted dystonias on the other body parts, severity of parkinsonism and relationship with levodopa treatment.

Results: BSP with or without AEO were more frequently observed in atypical parkinsonism (PSP, 70%; MSA-p, 11.2%; MSA-c, 8.9%) than in IPD (0.9%). Reflex BSP was observed only in atypical parkinsonism (4 MSA-p, 1 MSA-c and 2 PSP). BSP preceding parkinsonism (Pre-BSP) was observed mainly in atypical parkinsonism (2 MSA-p, 1 MSA-c, 1 PSP and 1 IPD). The presence of AEO was more frequent in atypical parkinsonism than in IPD, but isolated AEO was not detected. BSP related to levodopa ('off' symptom or 'peak-dose' effect) were observed only in IPD.

Conclusions: Reflex BSP, Pre-BSP and the presence of AEO may be a unique feature of atypical parkinsonism. BSP related to levodopa might be representative of IPD. No differences were found in the clinical features of BSP between MSA-p and MSA-c.

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Key Words : Blepharospasm, Apraxia of eyelid opening, Parkinsonism, Reflex blepharospasm

INTRODUCTION

Blepharospasm (BSP) is a focal dystonia characterized by repetitive involuntary sustained contractions of the orbicularis oculi muscle, causing spasmodic closure of the eyelids.¹⁻³ It is frequently found in association with

apraxia of eyelid opening (AEO).⁴ AEO has been described as a non-paralytic motor abnormality characterized by difficulty in opening the eyes at will in the absence of visible contraction of the orbicularis oculi muscle.⁴⁻⁶ When BSP occurs only in response to certain stimuli, such as a sudden visual threat or auditory or tactile stimulus, it is defined as reflex blepharospasm

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(R-BSP).^{3,7}

Most of these ocular symptoms, such as BSP, are not associated with another identifiable associated disease. In this case, they are referred to as primary or idiopathic.^{4,5,7} However, secondary BSP has occasionally been reported in patients with parkinsonism and in those with focal lesions in the basal ganglia, diencephalon, or brainstem, in addition to those with an ophthalmologic disorder.⁸⁻¹² AEO has been occasionally reported in patients with focal cerebral lesions and parkinsonism, particularly in those with progressive supranuclear palsy (PSP).^{6,13-15} Moreover, BSP and AEO have been reported as an coexisting dystonia in atypical parkinsonism, and are more commonly present in PSP.¹⁶ However, their clinical relationships are unclear, neither has it rarely been reported which disorder is related to several types of BSP.

Because there are no large clinical studies on several types of BSP such as reflex BSP (R-BSP) or preceding BSP prior to parkinsonism (Pre-BSP) in the literatures, we prospectively surveyed these symptoms in patients with parkinsonism. In the case of already existing BSP associated with parkinsonism, we retrospectively analyzed the characteristics and time intervals of BSP. We analyzed clinical features of BSP and AEO in patients with idiopathic Parkinson's disease (IPD), multiple system atrophy (MSA), and PSP. We subdivided MSA

into MSA-p (predominantly parkinsonism) and MSA-c (predominantly cerebellar) satisfying diagnostic criteria proposed by Quinn.¹⁷ Similarly, BSP was subclassified into R-BSP, Pre-BSP, and BSP combined with AEO, and these subtypes were then analyzed individually.

Our aims were to investigate the clinical characteristics of BSP and AEO associated with various types of parkinsonism and to find out if there is any clinical significance of BSP to differentiate parkinsonism including subtypes of MSA.

MATERIALS AND METHODS

1. Patient Selection

We enrolled 35 patients with BSP with or without AEO among 1113 patients with parkinsonism registered at the Movement Disorder Clinic of Samsung Medical Center from January 2002 to December 2003. Using the established diagnostic criteria for IPD,¹⁸ MSA^{17,19} and PSP,²⁰ the 1113 patients with parkinsonism were subclassified as having; IPD (913 patients), probable MSA (190 patients; 134 MSA-p and 56 MSA-c), or probable PSP (10 patients). We subdivided MSA into MSA-p (predominantly parkinsonism) and MSA-c (predominantly cerebellar) satisfying diagnostic criteria

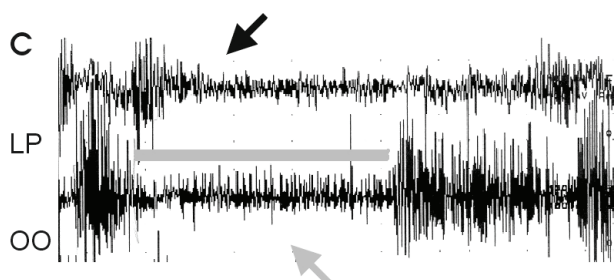
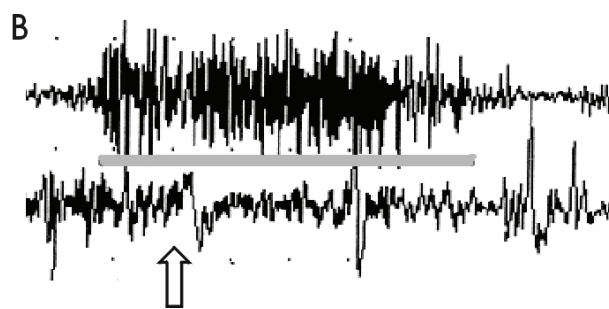
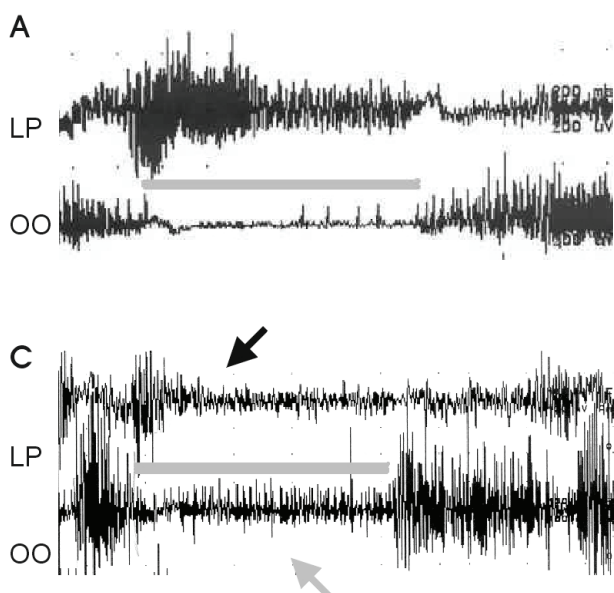


Figure 1. EMG of the levator palpebrae (LP) and orbicularis oculi (OO) in the normal individual (A), in the MSA-p patient with blepharospasm (B) and in the patient with blepharospasm and apraxia of eyelid opening (C). Comparing with normal finding (A), EMG showed a marked contraction of OO (white arrow) during eye opening (gray line) (B). During eye opening, OO inhibition was incomplete (gray arrow) and LP contraction was not sustained (black arrow) (C).

proposed by Quinn.¹⁷ We clinically diagnosed BSP using the established definition.^{3,7} In the case of those with coexisting BSP and parkinsonism, we retrospectively analyzed the characteristics and time intervals of BSP. For diagnosis of AEO, we used diagnostic criteria proposed by Lepore and Duvoisin.⁶ These included (i) no sign of ongoing orbicularis oculi contractions such as lowering of the brows beneath the superior orbital margin; (ii) marked frontalis muscle overaction during period of inability to raise eyelids; (iii) no ocular motor/ocular sympathetic nerve dysfunction and ocular myopathy. To confirm the presence of AEO with BSP, we performed electromyography (EMG) on the orbicularis oculi (OO) and levator palpebrae (LP) muscles (Fig. 1) in 13 patients who were diagnosed by above diagnostic criteria. We included patients with long-term follow up for maximum 24 months, full evaluations for parkinsonism, and a clinical diagnosis confirmed by at least two special neurologists based at Movement Disorder Clinic.

2. Periocular Electromyography

After getting the patient's informed consent, muscle activities from the orbicularis oculi and levator palpebrae were recorded by means of 2 channel- EMG (Nicolet Biomedical Inc., Medicine, Wisconsin, USA), using monopolar needle electrodes inserted into the left upper lid. Proper placement of the needles was confirmed by muscle activities at the opening and closing of the lid. Reference surface electrodes were spaced about 1cm apart from the active electrodes on the orbital bony prominence. A ground electrode was fixed in the middle of the forehead. Trials of opening and closing of eyes were repeated several times to acquire optimal signals. The EMG signals were amplified in a conventional manner, filtered (10-1,000 Hz), displayed on a memory oscilloscope, and analyzed offline.

3. Clinical analysis

We analyzed the clinical features of BSP and parkinsonism including demography, onset age, onset interval to BSP, clinical diagnosis of parkinsonism, severity of

parkinsonism, and relationship with levodopa treatment. Severity of motor symptoms of parkinsonism was evaluated by using motor UPDRS (part III of Unified Parkinson's Disease Rating Scale). To analyze the characteristics of BSP, we subclassified reflex BSP (R-BSP), BSP preceding parkinsonism (Pre-BSP), or BSP combined with AEO. R-BSP was defined when BSP occurred only in response to certain stimuli, such as a sudden visual threat or auditory or tactile stimulus.^{3,7} Pre-BSP was defined when BSP existed before presenting parkinsonism. Figure 1 showed EMG findings of EMG of BSP with or without AEO. Comparing with normal finding (Fig. 1-A), EMG showed a marked contraction of OO during eye closure (Fig. 1-B, 1-C). During eye opening, OO inhibition was incomplete and LP contraction was not sustained in BSP with AEO (Fig. 1-B). We also evaluated the coexistence of dystonia on other body parts.

4. Statistical analysis

All data are presented as means±standard error of mean (SEM). SPSS (version 12.0) program for windows (SPSS, Inc., Chicago, IL) was used for the statistical analysis. Sex differences and clinical characteristics of BSP data were analyzed using the Chi-square test. Onset age, onset interval to by parkinsonism, and severity of parkinsonism data were analyzed by using one-way ANOVA. Scheffe's test was used for *post hoc* comparisons. A *p* value of <0.05 was used as the criterion for statistical significance.

RESULTS

1. Clinical characteristics of BSP

Thirty-five BSP patients with parkinsonism (mean age, 61.2±7.2 years), 19 men and 16 women, were enrolled in the study. Of these 35 BSP patients, 8 (22.8%) were diagnosed as having IPD, 15 (42.9%) as MSA-p, 5 (14.3%) as MSA-c and 7 (20%) as probable PSP. Of the 913 patients with IPD 8 (0.9%) had BSP, 15 of 134 (11.2%) patients with MSA-p, 5 of 56 patients

Table 1. Demographic features of each form of parkinsonism

Patients	IPD	PSP	MSA-p	MSA-c
BSP / Total N.	8 / 913 (0.9%)	7 / 10 (70%) ^b	15 / 134 (11.2%) ^b	5 / 56 (8.9%)
Sex (M / F)	6 / 2 (364 / 549) ^b	6 / 1 (7 / 3)	11 / 4 (71 / 63)	0 / 5 (26 / 30)
Onset age (y) : initial Symptom	55.3±12.4	60.9±5.0	62.6±7.8	62.8±4.5
Onset interval (y) : to BSP	2.8±3.8	2.1±4.6	2.9±3.2	2.8±3.1
Motor UPDRS ^a	8.9±1.6	8.3±2.8	10.4±3.3	8.2±2.7

IPD: idiopathic Parkinson's disease, PSP: progressive supranuclear palsy, MSA: multiple system atrophy, BSP: blepharospasm, UPDRS: Unified Parkinson's Disease Rating Scale. ^apart III of UPDRS. Data represent mean±SEM. ^b $P<0.05$ by Chi-square test (for sex difference) and one-way ANOVA test (for other parameters).

Table 2. Demographic features and clinical significance of subclassification by BSP in parkinsonism

	BSP (n=35)	R-BSP (n=7)	Pre-BSP (n=5)	BSP+AEO (n=13)
Patients				
Sex (M / F)	19 / 16	5 / 2	4 / 1	7 / 6
Onset age (y)	61.2±7.2	57.3±11.2	48.7±14.2	59.7±10.2
Motor UPDRS ^a	9.6±3.0	10.2±3.7	9.8± 3.4	9.3±3.1
Parkinsonism				
IPD (N=913)	8	0	1	3
Atypical (N=200)	27 ^b	7 ^b	4 ^b	10 ^b
PSP (N=10)	7	2	1	3
MSA (N=190) (-p / -c)	20 (15 / 5)	5 (4 / 1)	3 (2 / 1)	7 (4 / 3)
MSA-P / MSA-C	15 / 5	4 / 1	2 / 1	4 / 3

BSP: blepharospasm, R-BSP: reflex blepharospasm, Pre-BSP: preceding blepharospasm prior to parkinsonism, BSP+AEO: blepharospasm with apraxia of eyelid opening, UPDRS: Unified Parkinson's Disease Rating Scale, IPD: idiopathic Parkinson's disease, PSP: progressive supranuclear palsy, MSA: multiple system atrophy, MSA-P: MSA parkinsonism predominant, MSA-C: MSA cerebellar predominant. ^apart III of UPDRS. Data represent mean±SEM. ^b $P<0.05$ by Chi-square test (compared atypical parkinsonism with IPD).

(8.9%) with MSA-c, and 7 of 10 patients (70%) with PSP had BSP. BSP was more frequent in PSP and MSA than in IPD ($p<0.05$). In terms of sex differences, in contrast to the lack of gender preference in MSA-p, BSP was more frequent in men than women in IPD and in PSP. BSP with MSA-c only affected women. With except of these findings, no other significant clinical demographic difference was observed among various types of parkinsonism (Table 1).

2. Clinical significance of subtypes of BSP for differentiating parkinsonism

According to BSP subtype, i.e., R-BSP, Pre-BSP, and

BSP with AEO, no significant differences were found between the parkinsonism types with respect to sex, age of onset, or severity of parkinsonism (Table 2). Seven of 35 BSP patients (20%) showed R-BSP. All R-BSP patients had been clinically diagnosed as having atypical parkinsonism (4 MSA-p, 1 MSA-c, and 2 PSP) (Table 2). Pre-BSP was observed in 5 of 35 BSP patients (14.3%: 1 IPD, 2 MSA-p, 1 MSA-c and 1 PSP), and was more frequently observed in atypical parkinsonism than in IPD ($p<0.05$). In our study, 13 of 35 patients with BSP (37.1%: 3 IPD, 4 MSA-p, 3 MSA-c and 3 PSP) showed combined AEO. The presence of AEO was more frequent in atypical parkinsonism than in IPD ($p<0.05$), but isolated AEO was not detected (Table 2).

Table 3. Other forms of dystonia combined with BSP in parkinsonism

Parkinsonism	Forms of combined dystonia			
	Cervical dystonia	Facial dystonia	Limb dystonia	Camptocormia
IPD (N=913)	0	0	1	2
Atypical (N=200)	4	1	0	1
PSP (N=10)	1	0	0	0
MSA (N=190) (-p / -c)	3 (1 / 2)	1 (1 / 0)	0	1 (1 / 0)

IPD: idiopathic Parkinson's disease, PSP: progressive supranuclear palsy, MSA: multiple system atrophy, unable to analyze statistically due to small number.

In terms of the relationship between BSP and levodopa treatment, BSP occurred as an 'off' symptom in two IPD patients and as a "peak-dose" effect in one IPD patient. In 3 IPD patients and in 1 MSA patient, BSP was improved by levodopa medication. However, one PSP patient presented aggravation of BSP after levodopa medication.

3. BSP combined with other types of dystonia in parkinsonism

Nine (25.7%) of 35 BSP patients also had other types of dystonia. Types of dystonia and the clinical diagnoses of these patients were as follows; 4 with cervical dystonia (1 MSA-p, 2 MSA-c and 1 PSP), 3 with camptocormia - meaning forward bending of truncal muscles (2 IPD and 1 MSA-p), 1 with limb dystonia (1 IPD), and 1 with facial dystonia (1 MSA-p) (Table 3).

DISCUSSION

In this study, we prospectively surveyed BSP in patients with parkinsonism. In cases with coexisting BSP and parkinsonism, we retrospectively analyzed the characteristics and time intervals of BSP.

BSP is considered to be one of the more common forms of focal dystonia in patients with IPD and atypical parkinsonism.²¹ In our clinical series, by noting the frequencies of BSP among each group with parkinsonism, BSP was found to occur more frequently in atypical parkinsonism, MSA, and PSP than in IPD. However, no significant difference was found between

the frequencies of BSP between subtypes of MSA, MSA-p and MSA-c.

In a recent report about BSP in IPD, gender was not found to be associated with the presence of BSP in IPD.¹² According to another case study about dystonia in MSA, dystonia was observed twice as frequently in women.²² In our study, BSP with MSA-c only affected women. Our study also showed that BSP patients were mainly men in IPD and PSP, but than the gender were similarly represented in MSA-p.

According to previous studies,^{4,6,23} AEO either combined with or without BSP may occur in parkinsonism, especially in PSP. In the present study, we found that 13 of 35 patients (37.1%) with BSP showed AEO, and that BSP with AEO was more frequently detected in atypical parkinsonism. Although AEO might occur in many neurological disorders, we did not observe isolated AEO associated with parkinsonism.

The subclassification of BSP into R-BSP, Pre-BSP, and BSP with AEO was found to be more clinically helpful for the diagnosis of atypical parkinsonism, such as MSA and PSP. The present study suggests that R-BSP is a unique feature of atypical parkinsonism, because it was observed only in atypical parkinsonism. Although one study reported that idiopathic BSP does not lead to a parkinsonian syndrome,²⁴ patients with Pre-BSP have a tendency to be diagnosed with atypical parkinsonism after long-term follow up. This finding contrasts with previous studies that presented patients with BSP only at advanced stage disease.^{11,25,26}

No differences were observed in the clinical features of BSP between MSA-p and MSA-c despite a previous report that dystonia is common in untreated MSA-p.²²

These findings support that BSP can be associated with any subtype of MSA.

The majority of previous studies have suggested that various types of dystonia can be observed in parkinsonism.^{16,21,22,27} We observed that other types of dystonia coexisted with BSP and AEO in parkinsonism. According to our study, even though we were unable to perform a statistical analysis due to small numbers, we presume that BSP combined with cervical dystonia or facial dystonia is more frequently related to atypical parkinsonism, whereas camptocormia or limb dystonia is more frequently related to IPD.

In terms of the relationship between BSP and levodopa treatment, we found that BSP might have occurred as an 'off' symptom or as a 'peak dose' effect of levodopa treatment in IPD. BSP that was improved by levodopa treatment was more frequently related to IPD, whereas BSP aggravated by levodopa treatment was more related to atypical parkinsonism. However, these suggestions were not statistically confirmable because of small patient numbers. Nevertheless, these relations are likely to be encountered in clinical medicine, and present a good clinical study topic for differential diagnosis in parkinsonism.

In conclusion, our study shows that BSP either with or without AEO is more frequently observed in atypical parkinsonism than in IPD, and suggests that R-BSP is a unique feature of atypical parkinsonism. In addition, our findings suggest that patients with Pre-BSP have a tendency to be diagnosed with atypical parkinsonism later, and that the presence of AEO indicates atypical parkinsonism. However, levodopa related BSP, including 'off' symptom, 'peak-dose' effect, or levodopa responsiveness were found to represent IPD rather than atypical parkinsonism. No differences were found between the clinical features of BSP in MSA-p and MSA-c.

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