ORIGINAL ARTICLE

Blepharospasm in Japan: A Clinical Observational Study From a Large Referral Hospital in Tokyo

M. Wakakura, A. Yamagami, and M. Iwasa

Division of Neuro-ophthalmology, Inouye Eye Hospital, Tokyo, Japan

ABSTRACT

Focal dystonia is regarded as a characteristic feature of blepharospasm. However, patients do not always present with motor symptoms. To clarify the clinical features of blepharospasm in Japan, we conducted a retrospective observational study involving a large population of patients from a single institution. Common symptoms included difficulty opening the eyes, photophobia, and ocular pain/irritation. Initial symptoms often occurred following the long-term use of psychotropics such as etizoram, benzodiazepines, and zolpidem (32% of patients). Our findings demonstrated that the clinical presentation of blepharospasm is heterogenous, and that understanding regarding sensory-dominant forms of the disease may be poor among practitioners in Japan.

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Introduction

Since the establishment of clinical guidelines for the diagnosis and treatment of blepharospasm by the Japanese Neuro-ophthalmology Society¹, the number of patients identified with both mild and severe forms of the disease has increased in Japan.^{1,2} Blepharospasm is generally regarded as a form of adult-onset focal dystonia; therefore, spasms of the orbicularis oculi muscle are seemingly essential for definitive diagnosis. However, patients do not always present with such spasms but may exhibit non-motor symptoms such as sensory, psychiatric, and cognitive impairments.^{1–3} Sensory symptoms may include severe photophobia^{1–7} and irritation/pain within ocular or periocular structures. As these symptoms can make it difficult to keep the eyes open, patients with blepharospasm often experience drastic reductions in quality of life (QOL).⁸

Relatively few cases of tardive blepharospasm (i.e., Meige syndrome) have been reported following prolonged use of neuroleptics.^{9,10} However, research has indicated that treatment with benzodiazepines and related psychotropics can induce milder cases of blepharospasm.^{11–13} Despite these findings, no studies to date have investigated differences or similarities in the clinical presentation

of drug-induced and benign essential blepharospasm. Furthermore, whether blepharospasm is associated with specific clinical features in the Japanese population remains unknown. Therefore, in the present study, we retrospectively analysed and compared data from a relatively large number of patients treated for drug-induced or essential blepharospasm at a large referral hospital in Japan.

Patients and methods

The present study included a total of 1,116 patients with blepharospasm (304 men, 812 women; mean age: 66.0 ± 16.7 years; age range: 15–90 years) who had made their first visit to the Division of Neuro-ophthalmology at Inouye Eye Hospital (Tokyo, Japan) during 2012. All patients had been diagnosed with blepharospasm in accordance with guidelines issued by the Japanese Neuro-ophthalmology Society.¹ The severity of blepharospasm was determined at the initial visit by one of three neuro-ophthalmologists, in accordance with our assessment criteria (Table 1a). Clinical information was retrospectively obtained from the clinical records system at our institution using an algorithm specific for blepharospasm. The diagnostic algorithm was developed based on patient reports, clinical findings including voluntary blinking assessment results

Table 1a. Determination of blepharospasm severity.

Grade 1. Negative for objective abnormality, based on a voluntary blinking score of 0–1 for Parts A and B, and scores of 0 on Test C.
Grade 2: Total score of 2–3 on Parts A and B; score of 0 on Part C.
Grade 3: Score of 2 on both Parts A and B and/or score of 1 on Part C.
Grade 4: Score of 3 on either Part A or Part B and/or score of 2–3 on Part C.
Grade 5: Unable to keep eyes open during in-person interview (>90%), in addition to Grade 4 criteria.

Table 1b. Voluntary blinking tests.

Please perform the following actions, and choose one of the four options that best describes your performance. Numbers 1 and 2 are indicative of abnormal blinking, while number 3 is indicative of the inability to blink.
Test A. Blink quickly and lightly (approximately 70 times per minute) without moving your eyebrows.
0: I can do it.
1: My eyebrows move; I blink only tightly.
2: I can't blink with the pace required; I blink too quickly.
3: I can't blink; I can't help closing my eyes when I try to blink.
Test B. Blink for 10 seconds as quickly and lightly as possible.
0: I can blink lightly more than 30 times in 10 seconds in good rhythm.
1: I can blink lightly about 30 times in 10 seconds with interruptions.
2: I can't blink lightly in good rhythm; I sometimes blink tightly.
3: I can't blink quickly and lightly.
Test C. Close your eyes tightly and then open them quickly. Repeat the action 10 times.
0: I can do it.
1: I can't open my eyes quickly several times and/or experience difficulty trying to open my eyes quickly.
2: I can open my eyes only slowly; or I close my eyes after the action for a while.
3: It is extremely difficult to open my eyes; or I can't perform the action 10 times.

(Tables 1b and 2), and history of psychotropic use. The study population represented 4.5% of all first-time patients during 2012 (total patients: 24,724).

History of psychotropic use has been carefully taken. When the psychotropics are prescribed during at least one month prior to the onset of

symptoms, then we judged the patient to be drug-induced blepharospasm.

Patient concerns/symptoms were categorised into the following three groups: motor disorders of the eyelids (clenching of the eyes, apraxia of eyelid opening, irregular voluntary blinking, and excessive blinking), sensory disorders or hypersensitivity (photophobia, irritation, pain, sensation of dry eyes, and other uncomfortable ocular and periocular symptoms), and psychiatric symptoms (mood disturbance, anxiety, irritability, insomnia).

We assessed the presence of mood symptoms associated with blepharospasm based on responses to a nine-item questionnaire (Table 3). In a sample of 27 age-matched control participants with mild cataracts or refractive error only, the mean total score was 2.7 ± 2.8 points. The normal range included scores within 1.5 standard deviations (SDs) of the mean, while scores greater than 7 points were considered indicative of mood disturbance.

To assess the effects of botulinum toxin A therapy in patients with blepharospasm, we conducted a separate analysis of all patients who had received such treatment during 2012 ($n = 1,403$, 326 men; 1,077 women; mean age: 66.3 ± 11.8 years; age range: 22–94 years). As some patients received botulinum toxin therapy several times, data were randomly chosen from a single visit during 2012.

Table 3. Mood changes associated with blepharospasm: self-report check list. Please read the sentences below, and rate yourself on each of the criteria by circling the number that best describes what you feel.

	Never	Sometimes	Often	Very often
1. I feel powerless/no energy.	0	1	2	3
2. I feel unable to do anything.	0	1	2	3
3. I do not want to meet with people who don't have knowledge of the disease.	0	1	2	3
4. I feel useless.	0	1	2	3
5. I tend to feel distressed.	0	1	2	3
6. I feel unfortunate to have gotten this disease.	0	1	2	3
7. I feel that I am not understood properly by the people around me.	0	1	2	3
8. I feel uneasy about my future.	0	1	2	3
9. My (general) physical condition has been disturbed by this disease.	0	1	2	3

Table 2. Blepharospasm self-report check list.

Please read the sentences below and check yes (Y) or no (N)
1. I blink a lot. Y N
2. I am sensitive to light when I go outside, or even when staying inside a building. Y N
3. I cannot keep my eyes open. (I prefer to keep my eyes closed.) Y N
4. I am always annoyed about my eyes: feeling dry, bleary, irritation or pain. Y N
5. I often bump into other people when I walk in a crowd. Y N
6. I have bumped into a parked car, a post, or a tree on the street. Y N
7. I usually stay indoors because of aversion to sunshine, wind, or stairs. Y N
8. I discontinued driving and/or cycling to be safe. Y N
9. I sometimes need to use my hands to open my eyes. Y N
10. I tend to close one of my eyes. Y N

The following data were collected for patients who had received treatment with botulinum toxin A (25 ~ 75 units in total dosage). Using the numerical rating scale (NRS, 0–10), patients were asked to rate the severity of photophobia, ocular or periocular irritation, ocular pain, difficulty opening the eyes, and other symptoms of concern. Patients were asked to rate their symptoms at each of the following time points: prior to the last injection, at the height of relief since the last injection, and prior to receiving the next injection (current visit). Patients were also asked to rate their overall level of satisfaction with botulinum toxin therapy as “very satisfied”, “satisfied”, “OK”, “unsatisfied”, or “very unsatisfied”. Data regarding the presence of any adverse effects since the start of botulinum toxin injections were also examined.

Statistical analysis was performed with SPSS Version 22.0 statistic software package.

Comparisons between groups were performed with analysis of Chi-square test. A value of $P < 0.01$ was considered statistically significant. Comparisons among the three groups were performed using Bonferroni’s method, and statistical significance was determined at an adjusted p -value < 0.0167 .

The present study was conducted in accordance with the tenets of the Declaration of Helsinki and received approval from the Institutional Review Board at Inouye Eye Hospital.

Results

Patient concerns and symptoms

There were no significant differences in age at onset, sex, comorbidities, response to treatment, mood disturbance, presentation/symptoms, time to diagnosis, quality of life, or severity between patients groups of essential blepharospasm and drug-induced blepharospasm.

The most common symptoms among all patients with blepharospasm were uncomfortable sensations within and around the eyes and inability to keep the eyes open due to severe photophobia and/or ocular pain. The chief and top three concerns among patients are displayed in Figure 1 ($n = 959$).

In 108 (9.7%) of 1,113 patients with available data, ocular symptoms manifested or developed immediately following surgical procedures. Among these 108 patients, 86 (80%) had undergone cataract surgery, nine (8%) had undergone eyelid surgery, five (5%) had undergone other types of ocular surgery, and eight (7%) had undergone extraocular surgery for cancer or neurological disease.

Sixty-two patients had undergone eyelid surgery for the treatment of age-related ptosis prior to the accurate diagnosis of blepharospasm. However, most of these patients ($n = 59$) deemed the results unsatisfactory.

In six patients, blepharospasm was associated with Parkinson’s disease or progressive supranuclear palsy. In 16 patients, blepharospasm was associated with various psychosomatic disorders including fibromyalgia syndrome, restless legs syndrome, irritable bowel syndrome, and glossodynia.

Figure 1. The frequency of chief and top-three concerns among patients ($n = 959$).

Duration between manifestation of initial symptoms and definitive diagnosis

Among 707 patients who could recall the time at which symptoms manifested, only 15 (2%) and 274 (39%) had received a definitive diagnosis of blepharospasm within 1 month and 2–12 months, respectively. In 43% of patients ($n = 306$), the time to definitive diagnosis ranged from 1–5 years. Moreover, the time to definitive diagnosis was greater than 5 years in 34% of patients ($n = 237$). Approximately two-thirds of patients needed to change doctors more than five times to obtain an accurate diagnosis. Common previous diagnoses by primary care physicians included dry eyes, age-related ptosis, eye strain of unknown cause, ocular myasthenia gravis, depressive disorders, and somatoform disorders. Previous doctors had provided correct diagnoses or suspected blepharospasm in only 19% of patients (172 of 884).

Severity of blepharospasm

Assessment results were available for 1,103 patients. Severity was regarded as Grade 1 in 8.3% of patients ($n = 94$), Grade 2 in 26.3% of patients ($n = 290$), Grade 3 in 34.5% of patients ($n = 380$), and Grade 4 ($n = 228$) and 5 ($n = 111$) in 30.7% of patients.

Influence of blepharospasm on QOL

Questions 5–9 in Table 2 were used to assess whether blepharospasm had influenced QOL in

each patient. Patients who answered “yes” to more than two questions were considered to have experienced significant decreases in QOL. Among all patients with essential and drug-induced blepharospasm ($n = 1,055$), 355 (33.6%) exhibited significant reductions in QOL. The number of patients with decreased QOL seemed to increase as the severity of the disease increased (Figure 2). Positive responses were most common for the following statements: I often bump into other people when I walk in a crowd (43%); I discontinued driving and/or cycling to be safe (32.5%).

Mood disturbance in patients with blepharospasm

Among all patients with essential and drug-induced blepharospasm ($n = 1,033$), mood disturbance was noted in 622 patients (60.2%), including 270 patients (40.1%) of essential blepharospasm and 215 patients (61.4%) of drug-induced blepharospasm. In contrast to findings observed for QOL, the number of patients with mood disturbance did not seem to rise in direct proportion to disease severity (Figure 3); however, the incidence of mood disturbance was significantly higher in patients with Grade 5 blepharospasm (68.1%) than in those with Grades 3 and 4 blepharospasm ($p < 0.0001$, Chi-square test). The incidence of mood disturbance was also significantly higher in patients with Grade 4 blepharospasm (64%) than in those with Grades 3 blepharospasm ($p < 0.0001$).

Figure 2. Percentage of patients (%) with decreased quality of life according to blepharospasm severity ($n = 1055$).

Figure 3. Percentage of patients (%) with mood disturbance according to blepharospasm severity (n = 1055).

Drug-induced blepharospasm

Thirty-six psychotropics were prescribed prior to the manifestation of the subjective symptom(s) in 359 patients (32.2% of 1,115 patients). A total of one, two, and three medications were prescribed to 86, 93, and 165 patients, respectively. In the remaining 15 cases, patients could not recall information regarding psychotropic use, or such information was absent from the medical records.

The most prescribed psychotropic medications were etizoram (112 of 359 patients, 31.2%), zolpidem (n = 84, 23.4%), and brotizolam (n = 83, 23.1%). This trend was also observed among patients receiving treatment with one or two psychotropic medications (Figure 4). The period between the initiation of psychotropic treatment and symptom onset ranged from less than 1 month to more than 20 years.

Figure 4. Psychotropics prescribed before the onset of blepharospasm. Each bar indicates the frequency among patients treated with a single, two agents, and the overall (total) frequency.

At the 18-month follow-up, data were available for 186 patients with suspected drug-induced blepharospasm. Among these, 93 patients exhibited improvement following the successful withdrawal of drug(s) (Group A). However, 39 patients exhibited no improvement following successful withdrawal (Group B), while 54 had refused to cease treatment or experienced unsuccessful withdrawal (Group C). There were significant differences in the psychotropics used among these groups. Five patients of Group A experienced completed remission after withdrawal without any further treatment, including botulinum toxin.

The average duration between the initiation of treatment with psychotropic medications and the onset of symptoms was 4.3 ± 5.7 years in Group A, 7.4 ± 4.9 years in Group B, and 9.9 ± 9.6 years in Group C. A significant difference in the duration between initiation of psychotropic treatment and symptom onset was observed between Groups A and B (Bonferroni's method, $p = 0.0146$), and between Groups A and C ($p < 0.0001$). However, no significant difference was observed between Groups B and C ($p > 0.05$).

Effects of botulinum toxin a treatment

Following the initial visit, 68.6% of patients underwent treatment with botulinum toxin A. Reasons for declining botulinum toxin treatment included difficulty scheduling regular visits, lack of understanding regarding the treatment, fear of needles, the desire to withdrawal from medications first, disagreement with the diagnosis,

consultation to obtain a second opinion only, and unknown reasons. NRS values in patients receiving botulinum toxin therapy were 6.2 ± 2.8 at the previous injection, 3.7 ± 2.3 at the height of relief following the previous injection, and 6.2 ± 2.9 at the current visit. NRS values at the height of relief were significantly lower than those reported at other time points ($p < 0.0001$, Wilcoxon signed-rank test).

Figure 5 shows the overall patient satisfaction ratings for botulinum toxin therapy based on the severity of blepharospasm. Among patients with Grade 5 and Grade 2 blepharospasm, 57.6% and 75.7% reported being very satisfied or satisfied with the treatment, respectively. There were no statistically significant differences in satisfaction ratings between patients with essential blepharospasm and those with drug-induced blepharospasm.

No adverse effects were observed in 73.6% of patients. However, 10.3% of patients experienced facial hardening, 7% experienced subcutaneous haemorrhage, and 1% experienced unilateral ptosis. Other adverse effects (1.8%) included periocular irritability, lacrimation, pain, skin wrinkling/loosening, and depression. No other physical or systemic effects were observed.

Other types of treatment in this cohort included the use of tinted glasses with or without crutches ($n = 403$), cosmetic tape ($n = 13$), occasional or continuous use of trihexyphenidyl hydrochloride ($n = 96$), *Yokukansan* powder (a traditional Kanpo medicine, $n = 61$), and clonazepam ($n = 12$). These

types of therapy were used either in conjunction with botulinum toxin treatment or in isolation.

Discussion

We presented mainly clinical features of essential blepharospasm and drug-induced blepharospasm. Although the latter occupied approximately one third, eyelid motor symptoms, visual or sensory disturbances around the eyes, and psychiatric disturbances could clearly be indistinguishable from essential blepharospasm.

In the present retrospective study, we clarified the common clinical features of blepharospasm in a large sample of Japanese patients. Patients with blepharospasm accounted for 4.5% of all first-time ophthalmic visits to our hospital. The rate of occurrence of this disease is more frequent than someone thought¹⁴ even supposing that as our institution is the largest referral centre for the treatment of blepharospasm in the Tokyo region and eastern Japan, but accurate diagnosis by general ophthalmologist and family practitioner seems to be difficult.

As blepharospasm is categorised as a form of focal dystonia, involuntary movements of the eyelids have been regarded as a characteristic feature of the disease. However, in the present study, movement disorders were not observed in all patients, although most reported symptoms such as excessive blinking and difficulty opening the eyes. In addition, our findings indicated that

Figure 5. Patient ratings of overall satisfaction with botulinum toxin therapy according to blepharospasm severity.

blepharospasm was associated with subjective sensory symptoms such as photophobia and ocular or periocular pain/irritation. Research has indicated that persistent photophobia is induced by impairments within several thalamic processing circuits, and that dysfunction of such circuitry may underlie the development of various pain syndromes.^{4,6} Thus, blepharospasm may be characterised by two primary phenotypes: a motor-dominant form comparable to focal dystonia and a sensory-dominant form that is often indistinguishable from somatic symptom disorder.

The most common symptoms reported by patients were difficulty opening the eyes due to persistent photophobia and/or ocular pain, suggesting that blepharospasm is associated with sensory-motor disintegration.^{15–17} Although it is difficult to conclude whether the motor system or sensory system is primarily involved in the mechanism of blepharospasm, our other study¹⁸ based on patients' statement indicates that a number of patients with drug-induced blepharospasm primarily or predominantly realise sensory disturbance such as photophobia and ocular or periocular pain/irritation. This results are compatible to the hypothesis in focal dystonia that abnormal processing of the somatosensory input in the central nervous system induces insufficient sensorimotor integration.¹⁹ Several resting-state functional MRI studies support the notion that primary blepharospasm is associated with decreased connectivity within the sensory-motor network.^{15,17,20}

In the present study, only 41% of patients received a definitive diagnosis within 1 year after the onset of symptoms. These findings indicate that symptoms associated with sensory-dominant blepharospasm may lead to diagnostic error or difficulty. In accordance with our findings, previous studies have reported that many patients are misdiagnosed with dry eyes, ocular surface disorders, ptosis, and pain disorders prior to receiving a final diagnosis of blepharospasm.^{1,2,21,22} If sensory symptoms are neglected during diagnostic procedures, patients may be diagnosed with age-related ptosis, which can result in unnecessary and ineffective eyelid surgery, as observed in the present study.

Taken together, our findings suggest that family doctors and general ophthalmologists exhibit a relatively poor understanding of the disease, especially in its mild forms. Similarly, a clinical analysis of 100 Chinese patients with blepharospasm revealed that the accuracy of initial diagnoses was only 10%.²²

Researchers have speculated that blepharospasm may be facilitated by a major lifetime stressor,^{23–25} indicating that environmental factors may play a role in the expression of the disease.

In the present study, 84 patients (7.7%) reported that symptoms began immediately after cataract surgery. This finding is in accordance with those of our previous report,²⁶ in which the patient developed blepharospasm following cataract surgery and was subsequently diagnosed with post-surgical maladaptation syndrome. Such findings highlight the need for eye surgeons to exercise caution during cataract surgery, as well as the need for future studies to identify risk factors for blepharospasm following such procedures.

The findings of the present study indicated that blepharospasm exerted substantial effects of mood and QOL, even among patients with milder forms of the disorder. While previous studies have also reported that blepharospasm significantly reduces QOL in affected patients,^{8,24,27} our results demonstrated that mood disturbances were not significantly associated with disease severity. In accordance with these findings, Fabbrini et al.²⁸ reported that depressive disorders are among the most common mood disturbances observed in patients with blepharospasm. The current law in Japan precludes patients with blepharospasm from applying for disability status. However, our findings suggest that such patients exhibit substantial visual impairment accompanied by psychiatric symptoms, highlighting the need for legal reform regarding this issue.

In the present study, the frequency of drug-induced blepharospasm was higher than that reported in our previous study involving patients who had undergone treatment with etizorham or benzodiazepines (32.2% vs. 20.9%).¹¹ However, we did not evaluate full medication history in the previous study, in which we relied on information provided voluntarily by the participants. In contrast, full histories were obtained for almost all

patients in the present study. Although psychotropic treatment prior to the onset of symptoms may have been unrelated to the disease in some patients, our findings strongly suggest that long-term treatment with psychotropics contributes to the development of blepharospasm. Indeed, improvement after withdrawal of the psychotropics was observed in a considerable number of patients in Group A. Improvement after the cessation of treatment with psychotropic agents appeared to be associated with the duration of medication use: Better outcomes were observed among patients with shorter durations of treatment (approximately <5 years). Our results further indicated that many patients with lengthy durations of treatment did not experience successful withdrawal from their medications, and that patients tended not to improve even following successful withdrawal.

Previous researchers have recommended the use of unidimensional scales for the assessment of pain intensity.³⁰ Similarly, numerical rating scales are frequently applied for the assessment of subjective concerns such as fatigue³¹ and patient satisfaction³² in various clinical fields. In the present study, we used a numerical rating scale to measure patient satisfaction with botulinum toxin A treatment. Our findings suggested that treatment with botulinum toxin A improved patient outcomes in all groups examined.

Our findings further highlight the need for clinicians to remain aware of the risk of blepharospasm when prescribing etizolam (a thienodiazepine) and benzodiazepines. However, the second most common medication prescribed to patients in the present study was zolpidem. Although zolpidem is a non-benzodiazepine with an unrelated chemical structure, it produces its effects via the benzodiazepine binding site at $\alpha 1$ -containing GABA_A receptors.³³ Therefore, the mechanism underlying the development of blepharospasm in patients treated with zolpidem may be consistent with that for other forms of drug-induced blepharospasm.

Independent of disease aetiology, botulinum toxin treatment was effective in 58–76% of our patients. However, these effects were less pronounced in patients with more severe forms of the disease. These findings highlight the need for early

diagnosis in patients with drug-induced or essential blepharospasm, which may prevent progression of physical and psychiatric symptoms. Although voluntary blinking tests are helpful in diagnosing blepharospasm, findings may be inconclusive in patients with mild forms of the disease. Our findings indicated that many patients with drug-induced blepharospasm reported sensory hypersensitivity only, making it difficult to obtain an accurate and timely diagnosis. To avoid misdiagnosis and oversight, we recommend that clinical criteria be updated to include “benzodiazepine-induced ophthalmopathy” or “benzodiazepine-induced ocular hypersensitivity”. These additional criteria may aid in the identification of patients with early-stage blepharospasm and the development of more accurate diagnostic procedures.

In conclusion, our findings demonstrated that the clinical presentation of blepharospasm is heterogeneous, and that understanding regarding sensory-dominant forms of the disease may be poor among general practitioners in Japan. However, further studies are required to more fully elucidate the clinical characteristics of blepharospasm, and to develop specific diagnostic methods for early detection of the disease.

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