Demographic and Clinical Features of Patients with Blepharospasm in Southern Taiwan: a University Hospital-based Study

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Abstract-

Purpose: Blepharospasm is a common focal dystonia. Severe blepharospasm has a disabling impact on work and everyday activities and may cause social embarrassment and catastrophic traffic accidents. This retrospective case-series study explored the demographic and clinical features and also the impact of blepharospasm on patients in southern Taiwan, where the climate is hot and humid and motorcycles are a popular mode of transportation.

Methods: One hundred eleven patients with essential blepharospasm who had been given botulinum toxin type A injections at a university hospital were enrolled. Data were collected from medical records and face-to-face interviews with the patients and their families.

Results: The mean age of onset was 58 years. The female/male ratio was 2.6:1. Eighty-one percent of our patients had seen an ophthalmologist at the beginning of their condition. Photophobia, sleep benefit, and diurnal change of clinical symptoms were present in over 80% of the patients. The initial diagnostic accuracy was 37% for ophthalmologists and 44% for neurologists. Myasthenia gravis caused most confusion in the differential diagnosis. Eighteen percent of the patients had been involved in motorcycle and car accidents. Regular botulinum toxin type A injections improved both eyelid spasm and subjective ocular symptoms in most patients.

Conclusion: Blepharospasm is under-recognized, and its differentiation from myasthenia gravis needs to be improved. Patients with blepharospasm are advised to receive regular botulinum toxin type A injections and to avoid riding motorcycles and driving cars.

Key Words: blepharospasm, botulinum toxin, eyelid, myasthenia gravis, diurnal change

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INTRODUCTION

Blepharospasm is involuntary repeated forceful contractions of the orbicularis oculi muscle of the eyelid; it frequently results in eyelid closure and visual disability. Blepharospasm is a focal dystonia that often begins

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insidiously and progressively worsens. It usually appears in the fifth to seventh decades of life and more frequently affects women [1,2]. Several lines of indirect evidence, including electrophysiological studies [3,4], structural [5-11] and functional brain imaging [12-15], and autopsy findings [16,17], suggest both a central origin and a dysfunction of the thalamus, basal ganglia, or brainstem.

Severe blepharospasm has a disabling effect on work and everyday activities and may cause social embarrassment and catastrophic traffic accidents. Until recently, there were only a few reports [1,2,18] on the demographic and clinical features of blepharospasm. This retrospective case-series study explored the demographic and clinical features and also the impact of blepharospasm on patients in southern Taiwan, where the climate is hot and humid and motorcycles are a popular mode of transportation. The findings of this study should increase the awareness of blepharospasm, increase the understanding of physicians of important differential diagnoses, and provide some practical advice for patients.

METHODS

This retrospective case-series study was conducted at the Botulinum Toxin Injection Special Clinic in National Cheng Kung University Hospital (NCKUH), which is both a primary care and referral center. NCKUH is located in Tainan City and is the only national university hospital in southern Taiwan. The author is the only doctor at NCKUH responsible for botulinum toxin type A (Botox; Allergan, Irvine, CA, USA) injections for patients with blepharospasm, hemifacial spasm, cervical dystonia, and other focal dystonias.

In the past 10 years (August 1999 to July 2009), 444 patients visited the Botulinum Toxin Injection Special Clinic: 203 with hemifacial spasm, 173 with blepharospasm, 52 with cervical dystonia, and 16 with other focal dystonias (e.g., writer's cramp, oromandibular dystonia). The target population of this study was patients with essential blepharospasm. Essential blepharospasm refers to involuntary eyelid spasms that have no obvious underlying cause, is a focal dystonia, or is part of the manifestations of generalized dystonia. Sixty-two of the 173 patients with blepharospasm were excluded from this study for the following reasons: no botulinum toxin type A injection or loss of follow-up (n = 35), psychiatric disorders (n = 11), parkinsonian syndrome (n = 9), parkinsonism with dementia (n = 3), multiple strokes (n = 2), dementia (n = 1), and amphetamine abuse (n = 1). We did not routinely check serum ceruloplasmin and copper or 24-h urine copper to rule out the possibility of Wilson's disease as a cause of secondary blepharospasm. No genetic test was done for the enrolled patients. One hundred eleven patients were enrolled in this study. Data were collected from medical records and face-to-face interviews with the patients and their families. This study was approved by the Institutional Review Board of NCKUH.

The Taiwan National Health Insurance system reimbursed the hospital for each injection of 40 units of botulinum toxin type A each time, and reimbursed each patient for three injections per year. Each patient was put on an initial regimen of three 40-unit injections per year. The dose was adjusted if the beneficial effect lasted less than 3 months. Patients had to pay for the additional units by themselves if they received more than 120 units per year.

RESULTS

Eighty women (72%) and 31men (28%) participated in this study. The female:male ratio, was 2.6:1. The mean age of onset was 58±10 years (range, 29-84 years). The mean duration of follow-up was 4.7±3.0 years (range, 0.5-10 years). The onset of blepharospasm before or at 40 years old was 5%, between the ages of 41 and 50 was 16%, between the age of 51 and 60 was 35%, and older than 60 years was 44%. Thirty-three of the 111 patients (30%) included in this analysis had concomitant orofacial-cervical dystonia.

The three most frequent complaints at presentation were difficulty in opening the eyes, increased blinking, and involuntary forceful closure of the eyelids (Table 1). Only 12 (11%) of the patients spontaneously complained of photophobia, but on questioning, 97 (87%) of the patients had photophobia. Sixty-nine (62%) of the

Table 1. The presenting symptoms of patients with blepharospasm (111 patients)

Symptom	No. of patients*
Difficulty in opening the eyes	57
Increased blinking	46
Involuntary forceful closure of the eyelids	31
Ocular soreness	30
Droopy eyelid/ptosis	26
Dry eyes	21
Watering eyes	17
Photophobia	12
Peri-orbital/ocular pain	11
Itching	10
Grittiness	7
Twitching of the lower eyelids	4
Ocular fatigue	4

*Many patients had more than one symptom at presentation. Photophobia was one of the chief complaints in 12 (11%) of the patients, but on questioning, 97 (87%) of the patients had photophobia.

patients said that their eyelid spasms or ocular symptoms had starting on one side, 24 (22%) had bilateral involvement at the beginning, and the other 18 (16%) were uncertain about unilateral or bilateral onset.

Ophthalmologists were the physicians most frequently consulted first by the blepharospasm patients (90 cases, 81%) (Table 2), and neurologists were second (18 cases, 16%). Those who first saw an ophthalmologist had initial diagnoses of dry eye syndrome in 34 (38%) patients and blepharospasm in 33 (37%) patients. For 15 of these 67 patients, and for three others (18/90, 20%), myasthenia gravis was a differential diagnosis that needed to be excluded. Of those 18 patients who saw a neurologist at the beginning, 8 (44%) were diagnosed with blepharospasm and 4 with myasthenia gravis. Myasthenia gravis was also the initial tentative diagnosis for the 1 patient who initially consulted an internist. In summary, 23 patients of the 111 patients (21%) had been suspected of having myasthenia gravis at the beginning. Eighteen patients received a single or a combination of tests related to myasthenia gravis. These tests included a repetitive nerve stimulation test in 18, an acetylcholine receptor antibody in 6, an edrophonium or neostigmine test or a therapeutic trial with pyridostigmine in 4, chest computed-tomography in 4, and single fiber electromyography in 2.

Many exacerbating factors or activities were reported by the patients. In order of decreasing frequency, they were: bright light, wind, stress, watching television, driving, changes in the weather, eating, talking, insomnia, walking, reading, fatigue, looking down, mental activity, a hot environment (such as working in the kitchen or a bakery fireplace), and sweating. To the contrary, the relieving factors or the maneuvers used to improve symptoms were (in order of decreasing frequency): rest or sleep, splashing water on the face or placing a wet towel on the eyelids, relaxing and gently closing the eyes, touching or massaging the periorbital areas, opening the mouth, wearing sunglasses, covering or closing one eye, talking, looking down, eating, grinding the teeth, pursing the lips, extending the neck, and swimming.

Forty-nine (44%) of the patients had both photophobia and aerophobia, 48 (43%) had photophobia without aerophobia, and 14 (13%) had neither photophobia nor aerophobia. Bright light from various sources induced irritating ocular discomfort and increased spasms, and made it more difficult for the patients to open their eyes. Patients tended to pull down the window shades or close the curtains, reduce the brightness of television and computer screens, and dim the rooms they occupied by switching off some lights. Bright light also prevented patients from going outdoors by themselves during the day and at night. Head winds had an effect similar to that of light on the blepharospasm symptoms in 49 (44%) of the patients. Patients noticed that using a wind shield or visor while riding a motorcycle helped relieve their symptoms.

Sleep benefits and diurnal changes of blepharospasm symptoms were reported in 90 (81%) of our patients. Patients felt better in the morning and after rest or sleep. The sleep benefits lasted from several minutes to half a day. It was easier for patients to open their eyes in the morning. The symptoms gradually became worse in the afternoon and evening. Most of the patients said that the

season did not have a significant influence on their symptoms.

Functional blindness occurred in 85 (77%) of our patients. These patients had difficulty leading an independent life and sometimes had to leave their jobs because of the visual disability. Bumping into people while walking, especially someone of the opposite sex, usually caused great social embarrassment. Sixty-one (55%) had been involved in accidents. Twenty of the 61 patients had been in motorcycle or car accidents. The car accidents were mainly rear-end collisions. The most severe injuries were caused by motorcycle accidents, and 3 of the 20 patients involved in motor vehicle accidents were hospitalized (1 femoral fracture, 1 blunt abdominal injury with internal bleeding, and 1 cervical cord injury with quadriparesis). The injuries reported by most patients included ecchymosis, burns, abrasion, lacerations, and sprained ankles.

Anticholinergics (e.g., trihexyphenidyl, biperiden), clonazepam, and baclofen were prescribed most frequently for our patients. Twenty-one (19%) of our patients reported a mild-to-moderate beneficial effect, and they preferred to continue the oral medications even after botulinum toxin type A injections. However, for most patients, the oral medications usually did not work, or they were frequently precluded because of their side effects (in order of decreasing frequency): daytime drowsiness, dry mouth, unsteady gait, blurred vision, memory impairment, dizziness, lethargy, and confusion. Eleven (10%) of the patients reported that the oral medications helped their nocturnal sleep and thus improved the eyelid spasms the next day.

The mean duration of botulinum toxin type A treatment was 5.1±3.1 years (range, 0.4-10 years). The mean number of injections was 15.6±9.5 (range, 2-37). The mean dose per treatment was 42.2±4.6 units (range, 35-60 units). Forty-four (40%) patients needed a mean dose over the 40 units reimbursed by the Taiwan National Health Insurance system. The mean interval between injections was 4.1±1.5 months (range, 2.4-6.6 months). The duration of effect for botulinum toxin type A 40 units was longer than 3 months in 64 (58%) of the patients. The daily cost of botulinum toxin type A treatment was 29.6±13.7 NTD (New Taiwan dollars) (range, 15.5-51.1 NTD). The primary side effect of the botulinum toxin injections was local bruising.

For those patients who had ocular symptoms (dry eyes, watering eyes, soreness, itching, grittiness, and periorbital or ocular pain), the eyedrops either had no effect or had a mild effect lasting less than 30 minutes. Eighty (88%) of the 91 patients with ocular symptoms reported that botulinum toxin type A injections had marked and long-lasting effects (over 2 months) on their ocular symptoms. After a botulinum toxin type A injection, patients rarely needed to see an ophthalmologist, and they usually did not need eyedrops. When the effect of the botulinum toxin type A wore off, patients experienced increased eyelid spasms and ocular symptoms. The eyelid spasms and ocular symptoms waxed and waned in the same pattern, and both responded to repeated botulinum toxin type A injections.

DISCUSSION

Blepharospasm is the most common focal dystonia in our hospital. The distribution of age at onset, female preponderance, and the exacerbating or relieving factors are similar to those reported in the literature [1,2,18]. Sixty-two percent of our patients had unilateral symptom onset, which is much higher than the 19.7% and 25.5% reported by two other studies [1,2]. The study methods of these two reports were based on a questionnaire and supplemented with a telephone interview or a clinic visit when answers to questions were difficult to interpret. The present study used the medical records and face-to-face interviews to collect the demographic and clinical data. For patients with a long history of blepharospasm, we believe that the medical records may be more accurate than the patients' recall memory. The different study methods may partly account for the discrepancy in the proportions of patients with unilateral onset. An ethnic effect on the mode of onset could be another possibility. The predominantly unilateral onset and the later appearance of asymmetric decreased palpebral fissures made the differential diagnoses of myasthenia gravis and hemifacial spasm most common in this series (Table 2).

Table 2. Physician consultation and initial diagnosis (111 patients)

Physicians and initial diagnosis	No. of patients
OPHTHALMOLOGISTS	90
Dry eye syndrome*	34
Blepharospasm*	33
Unknown	10
Myasthenia gravis	3
Hemifacial spasm	3
Dermatochalasis	2
Nasolacrimal duct obstruction	2
Allergic conjunctivitis	1
Trichiasis	1
Cataract	1
NEUROLOGISTS	18
Blepharospasm	8
Myasthenia gravis	4
Hemifacial spasm	3
Unknown	3
NEUROSURGEONS	1
Hemifacial spasm	1
PLASTIC SURGEONS	1
Dermatochalasis	1
INTERNISTS	1
Myasthenia gravis	1

*For the 67 patients who had an initial diagnosis of either dry eye syndrome or blepharospasm, myasthenia gravis was considered a differential diagnosis that needed to be excluded in 15 patients.

Dry eye syndrome is a common ophthalmological diagnosis for patients with blepharospasm. One study [19] that used the Schirmer tear test to compare the tear secretion of 57 patients with blepharospasm, 50 patients with hemifacial spasm, and 107 controls, found a significant decrease of tear secretion in the blepharospasm group, and that only 50% of blepharospasm patients with a Schirmer measurement of less than 5 mm complained of dry eye. The study concluded that the correlation between the Schirmer measurement and dry eye symptoms is poor. Eighty-seven percent of our patients had photophobia. One study [20] showed that patients with blepharospasm were more light-sensitive than controls. The light sensitivity of those with blepharospasm can be improved by wearing tinted spectacles, but they remain more light-sensitive than those without blepharospasm who do not wear tinted spectacles.

Myasthenia gravis was the most frequently confused diagnosis in this study and in Jankovic et al. [18]. The pretarsal fibers of the orbicularis oculi muscle close the eye in a fashion that mimics ptosis. The common features for both myasthenia gravis and blepharospasm include predominant eyelid involvement, ptosis with unequal palpebral fissures, sleep benefit, diurnal change, relief by rest or local cold water packing, excessive blinking, and photophobia. The presence of ocular surface irritation symptoms and the concomitant lower facial or cervical dystonia favor blepharospasm. The presence of diplopia before a botulinum toxin injection, weakness of the bulbar muscles, neck muscles, or limb muscles, and the demonstration of a neuromuscular junction disorder by pharmacological, electrophysiological, and immunological tests favor the diagnosis of myasthenia gravis. Differentiating these two diseases is important because they require different clinical workups and therapeutic plans. Patients with myasthenia gravis presenting with chronic blinking that mimicked blepharospasm have sometimes been given inappropriate treatment [21]. Comorbid myasthenia gravis and blepharospasm in a patient is quite rare [22-24]. Myasthenia gravis should be optimally treated before considering using botulinum toxin in patients with coexisting myasthenia gravis and blepharospasm [22].

Six of the patients in the present study were initially suspected of having hemifacial spasm. The frequent unilateral onset and the initial involvement of the lower eyelid make it difficult to differentiate these two conditions in their early stages. Also, the presence of photophobia in some patients with hemifacial spasm adds to the confusion. The presence of ear click due to the contraction of the stapedius muscle, the persistence of facial twitching during sleep [25], and the demonstration of ephaptic transmission with a blink reflex study support a diagnosis of hemifacial spasm. Patients with hemifacial spasm usually do not have ocular surface irritation symptoms. The spasm remains unilateral in hemifacial spasm, whereas in blepharospasm, there is nearly always bilateral involvement within several months. The high

proportion (62%) of unilateral onset of blepharospasm and the over-representation of hemifacial spasm in the Asian population [26] make it important to differentiate these two diseases in the early stage. The correct diagnosis can preclude unnecessary and potentially harmful microvascular decompression surgery.

Several findings from this study should be highlighted: (a) motorcycle and car accidents associated with blepharospasm can be catastrophic for the patients themselves or for others; (b) the low accuracy (37% for ophthalmologists, 44% for neurologists) when initially diagnosing patients with symptoms of blepharospasm needs to be improved, because blepharospasm has a disabling impact on jobs and everyday life activities; (c) the ability to differentiate blepharospasm from myasthenia gravis needs to be improved, because local botulinum toxin injection improves blepharospasm but worsens myasthenia gravis; and (d) although unilateral onset and initial lower eyelid involvement may suggest a diagnosis of hemifacial spasm, microvascular decompression surgery should be deferred until the diagnosis is confirmed.

Some practical advice for patients is: (a) maintain good sleep quality and quantity, and take rests as needed (sleeping pills may be used if indicated); (b) mornings are preferable for outdoor activities; (c) use tinted spectacles or hats with a wide visor when going outdoors or exposed to a bright environment, and use headband to reduce the irritative effect of sweat on the eyes; (d) avoid riding a motorcycle, but if motorcycle riding is necessary, reduce the speed and use a well-ventilated full-face helmet; (e) receive regular botulinum toxin type A injections; and (f) try the relieving factors listed in the Results section.

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