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Dry-eye Syndrome in Benign Essential Blepharospasm

Syndrome de sécheresse oculaire dans le blépharospasme essentiel

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Résumé

But. Evaluer l'importance de la sécheresse oculaire dans le blépharospasme essentiel.

Matériel et méthode. Etude rétrospective, consécutive, des tests de Schirmer I portant sur 144 patients atteints de blépharospasme essentiel soit sur 288 yeux. Les scores ont été analysés en fonction du sexe, de l'âge des patients et de la sévérité du blépharospasme.

Résultats. Les 144 patients (moyenne d'âge: 68.3 ± 11.5 ans) répartis en 110 femmes et 34 hommes, (76% de femmes) ont un test de Schirmer I diminué en moyenne à 5.9 ± 7.5 mm (median: 2.5 mm); 86.8% des patients avaient un Schirmer I < 15 mm et 75% un Schirmer I < 10 mm sans différence statistiquement significative entre les hommes et les femmes ($P = 0.27$), bien que le blépharospasme soit fortement corrélé au sexe féminin ($P = 0.0044$). La sévérité du syndrome sec oculaire n'était pas corrélée à l'âge, ni au sexe (pour les hommes $r = -0.22$, $P = 0.22$ et pour les femmes $r = -0.067$, $P = 0.49$), ou à la sévérité du blépharospasme ($P = 0.15$)

Conclusion. Le syndrome de sécheresse oculaire est fortement corrélé au blépharospasme essentiel indépendamment de l'âge, du sexe et de la sévérité du blépharospasme. Le traitement du syndrome sec oculaire est nécessaire mais ne soulage pas le blépharospasme qui ne répond qu'aux injections trimestrielles de neurotoxine botulique A dans le muscle orbicularis oculi.

MOTS CLES:

blépharospasme essentiel ; syndrome sec oculaire ; sécheresse oculaire ; larmes ; test de Schirmer I ; douleur.

SUMMARY

Purpose: To determine the reality of dry eye syndrome in benign essential blepharospasm.

Design: Retrospective consecutive case series

Participants: One hundred and forty-four patients with benign essential blepharospasm.

Methods: All subjects had Schirmer I tear tests. Those scores were analysed as a function of patient age, sex, and blepharospasm severity.

Main Outcome Measures: Individual Schirmer-test scores in both eyes of all patients (288 eyes)

Results: A total of 144 eligible subjects (mean age $\pm$ SD: 68.3 $\pm$ 11.5 years; 76% females) were evaluated. Benign essential blepharospasm was significantly associated with female sex ($P = 0.0044$). The mean Schirmer-test value was 5.9 $\pm$ 7.5 (median: 2.5) mm; it was <15 mm for 86.8% of the patients and <10 mm for 75%, with no difference observed between men and women ($P = 0.27$). Dry-eye syndrome severity was not correlated with age at the diagnosis, for men ($r = -0.22$, $P = 0.22$) or women ($r = -0.067$, $P = 0.49$), or benign essential blepharospasm severity ($P = 0.15$), but was strongly associated with benign essential blepharospasm independently of age, sex or blepharospasm intensity.

Conclusion: Dry-eye syndrome and benign essential blepharospasm were so strongly linked, independently of age, sex or BEB severity, that when this sign is absent, the diagnosis of benign essential blepharospasm should be reconsidered. The useful symptomatic treatment of dry eye will not cure the blepharospasm or the ocular pain and specific treatment for blepharospasm is required, i.e., quarterly injections of botulinum toxin A into the orbicularis.

Key words: benign essential blepharospasm, dry-eye syndrome, Schirmer I tear test, tear, pain

Abbreviations: BEB : benign essential blepharospasm, DES : dry-eye syndrome.

Benign essential blepharospasm (BEB) is a rare, underdiagnosed orphan disease (ORPHA93955-MIM 606798 of the Orphanet catalog) that affects about 3.5/100,000 inhabitants, according to a multicenter, epidemiologic European study [1]. That prevalence was confirmed more recently (32.2/1,000,000 inhabitants), by a study conducted in Sardinia that was meaningful because of the geographical location of the island [2] but BEB probably remains underestimated.

Most patients initially complain of dry, burning eyes and excessive blinking [3]. They usually consult their general practitioners first, before being referred to ophthalmologists or neurologists.

Notably, the pathogenic mechanism underlying BEB remains unknown, although it is considered as a dystonia, or neurologic movement disorder in which prolonged muscle contractions are responsible for twisting and repetitive movements, of central neurological origin. Muscular spasms treatment by botulinum neurotoxin's injection does not exclude the treatment of dry-eye syndrome (DES), which has been considered as a possible initiating cause of BEB [4]

The potentially debilitating severity of functional symptoms during facial dystonia, particularly BEB, led us to analyze the frequency of the DES associated with it. This latter banal clinical sign is not routinely diagnosed in facial dystonia [3-5]. Facial dystonia of central origin that affects both eyes [6-8] includes BEB, Meige syndrome and eyelid-opening apraxia. We limited our study to semi-quantitative tear analysis using Schirmer I test in BEB.

We examined whether the degree of palpebral spasm severity, assessed using previously described scales [9] was linked to DES severity. Because the etiological hypothesis of DES based on hormonal dependence [10] advanced that lacrimal secretion diminished after menopause [11,12] and with aging [13-15], we evaluated whether BEB women were more affected than men by DES.

Patients and Methods

Patients

One hundred and forty-four consecutive patients with BEB, who accepted to undergo semi-quantitative tear analysis with the Schirmer I test, were included. Informed consent was obtained from each subject in accordance with the tenets of the declaration of Helsinki. The following information was collected: age; sex; date of dystonia onset and its severity; and time interval between the first clinical signs of BEB and its definitive diagnosis. We also collected personal and family medical histories.

BEB was classified in 4 intensity levels (Table 1). Level 1 BEB was considered not to be very incapacitating but was manifested by too frequent blinking, with a short period of involuntary palpebral occlusion, but the patient was still able to go about his daily life: safely drive a car, watch a film on television or at the movies, cross the street alone, walk alone outside, read newspapers or a book, or do any usual visual activity at close range, move around at home or outside, and perform domestic tasks. At level 2, the orbicularis spasms occur several times daily, are visible to others, make it difficult to look at a screen for a long period of time (computer, television or films cannot be watched in their entirety but comprehension remains possible). A patient with level 3 BEB cannot longer drive, hesitates to leave the house alone, reading papers becomes too difficult and viewing a film becomes impossible. Level 4 BEB means the total loss of autonomy: added to the aforementioned handicaps, the impossibility to go out or cross the street alone; the patient bumps into usual objects (doors, tables...), with frequent loss of balance leading to falls and even fractures.

Methods

DES severity was quantified with the Schirmer I test. Without topical anaesthesia or artificial tears from the evening before the test, a strip of Whatman filter paper was placed in the inferior conjunctival fornices for 5 minutes, starting with the right eye. Results were reported in length (mm) of wetting strip. Schirmer I test was done on the day of a routine consultation, before any new injection of botulinum toxin from three months. The analysis concerned all 144 BEB patients, for a total of 288 eyes.

Statistical Analysis

The statistical analyses included both descriptions and tests. The significance level was set at 5%. The mean $\pm$ standard deviation values of the Schirmer I-test scores for both of the patient's eyes affected with BEB were used in the analysis. The qualitative variables were compared using the chi-square test or Fisher exact test, as appropriate. The quantitative variables were compared with the bilateral nonpaired *t*-test, paired *t*-test, Kruskal–Wallis test or Pearson correlation coefficient. The statistical analyses used Statview software v5.0 (SAS Institute Inc, Cary, NC).

Results

The mean age of the patients was 68.3 ± 11.5 years, 68.7 ± 11 years for women and 66.8 ± 13.2 years for men, with a F/M sex ratio of 76,39% (110/34). A very strong statistically significant association ($p = 0.0044$) was found between BEB and female sex (Table 2).

The mean lacrimal secretion absorbed by Schirmer test filter papers was 5.79 ± 7 mm and the median lacrimal secretion was 2.5 mm [range: 0–31]) (Fig 1). These patients' lacrimal secretions

did not differ significantly between their left and right eyes (0.34 mm; $p = 0.46$). That nonsignificant difference can be explained by the more severe left-sided pain and palpebral spasm as a consequence of having placed filter-paper strip first in right conjunctival fornix.

All women in this study were menopausal. Although a very strong association exists between BEB and women, the lacrimal secretions (Schirmer test) of women and men with BEB did not differ significantly (nonpaired t -test, $p = 0.27$).

Also, we found no significant correlation between DES severity, as assessed by the Schirmer I test, and age at BEB diagnosis (Fig 2), with mean values for women 5.4 ± 6 mm ($r = -0.067$, $p = 0.49$) and 5.8 ± 7.5 mm ($r = -0.22$, $p = 0.22$) for men.

Among the 144 patients studied, 125 (86.8%) have Schirmer I-test values <15 mm, and 110 (76.4%) have Schirmer I-test values <10 mm, making this symptom a frequent associated sign, strong and reliable marker for the clinical diagnosis of BEB.

For BEB patients, no statistically significant association (Kruskall–Wallis test, $P = 0.15$) was found between Schirmer I tests and the degree of spasm severity.

BEB remains under diagnosed. Moreover, the mean time between the first signs of the disease and its diagnosis was 43 ± 69.5 months (median: 22.5 [range: 1– 648]).

Discussion

BEB is a recognized orphan disease with a European prevalence of 3.2 to 3.6/100,000 [1,2]. It is a dystonia of central origin with non-elucidated etiology. BEB is currently called idiopathic. The observations described by Evinger et al [4], led them to conclude that DES played a triggering role in BEB onset, with hypersensitivity to stimuli causing a blinking reflex in these patients. The pain induced by dry eye (decrease of tear break-up time and dry punctuate keratitis) serves as stimulus to exaggerate nervous system response and would increase frequency, amplitude and intensity of the blinking. The trigeminal blinking reflex then would become

hyperexcitable, with the loss of nervous system ability to adjust blinking to the stimulus.

However, other authors [6,16], asserted that treating DES with artificial tears failed to attenuate BEB and concluded that no etiological relationship existed between DES and BEB, which concurs with our experience.

At lower BEB grade, an injection of botulinum toxin alone was enough to provide relief for our patients who can forget eye drops instillations. Also, our patients had to wait 2 years in median to obtain a diagnosis of BEB, while they were treated in this meantime with artificial tears. That symptomatic therapy of DES did not provide pain relief or attenuation of the orbicularis spasm. Nor did artificial tears to prevent the development of BEB or its possible worsening towards Meige syndrome [7]. On the other hand, ophthalmologic follow-up of the DES seen in systemic diseases (Sjögren syndrome, rheumatic diseases, lupus, sarcoidosis, etc...) showed no progression towards BEB. All these clinical observations led us to consider BEB as a primary neuropathy, in which 87% of the BEB patients have a DES.

The frequency of DES in BEB was often mentioned but rarely statistically analyzed [3, 6]. In our study, Schirmer I-test scores were <15mm for 86.8% and <10 mm for 76.3% of our 144 BEB patients so for 288 eyes of the study. In Martino's series of 165 BEB patients, 35,7% had DES with Schirmer <10mm [17]. Our data are similar to those reported in the Australian study. Sixty-nine per cent of BEB patients had Schirmer I-test scores <10 mm [5]. The Australian patients' mean Schirmer-test scores were 7.9 ± 8.9 mm vs. 13.4 ± 10 mm for their age- and sex-matched control group [5], similar to our patients who had more severe DES, with a mean Schirmer-test value of 5.9 ± 7 (median: 2.5) mm and no significant score differences between their left and right eyes. A recent Korean study performed on 23 patients, revealed Schirmer I test at 4.92 ± 3.52 mm before neurotoxin injection [18].¹⁷ A Chinese study realised on 40 BEB chineses patients, revealed a mean Schirmer I test at 6.53 ± 1.81 mm. This Chinese study confirme femine

predominance (65% women) and medium age at onset was $58 \pm 8,5$ years old [19]. For Jankovic and Ford [6] the DES of women with BEB was strongly correlated with Sjögren syndrome, and the detection of anti SS-A and SS-B autoantibodies, which would indicate a systemic disease associated. This interesting point has to be confirmed but the more we learn about BEB the more it appears as a complex disease.

Although artificial tears obtained real pain relief from DES, they had no effect on BEB. Restoring correct lacrimal cover do not relieve BEB [6]. That observation held true for all our BEB patients who had been treated with artificial tears before being referred. None of them described any BEB regression with any local treatment other than quarterly injections of botulinum toxin into the orbicularis [16]. Thus, the origin of the BEB is not apparently in DES, even though DES was present in pathognomonic manner in BEB.

To discern the real BEB etiology, a cohort study on isolated DES (without BEB) will have to be conducted and their systematic progression towards BEB verified. Notably, for our patients with Sjögren syndrome, with attentive monitoring and close collaboration between rheumatologists and ophthalmologists, we systematically did not observe any progression towards BEB. Hence, the debate concerning BEB etiopathogenesis is still open.

Pain seems to be more debilitating in BEB than other pathologies responsible for dry eye. Independently of DES, this hyperalgia brings us back to the hypothesis emitted by Evinger et al [4] that BEB resulted from hypersensitivity to the stimuli triggering a tonic blinking reflex in these patients. BEB patients had more severe photophobia than patients with isolated DES.

We never found a significant relationship between the severity of eye dryness measured by Schirmer I test and the BEB intensity grade, excluding the hypothesis of the dryer the eye, the longer and more tightly the eyelids were closed. Daily discomfort and even pain were not associated with the semi-quantitative severity of the DES or with the severity of BEB blinking.

This absence of association was not specific to BEB and has been observed in many patients with DES [20]. In our experience, blepharospasm appeared first and was initially of cerebral central origin. When BEB is diagnosed, it is almost always associated with concomitant DES, but the latter is not the etiopathology of the orbicularis spasm.

The severity of lacrimal deficiency and its very high frequency in BEB are predominant, masking the orbicularis-spasm symptoms, perhaps leading to misdiagnosis. The sensation of dry eye or ocular burning was mentioned by all our patients and was relieved by voluntarily closing the eyes. Patients did not differentiate between the voluntary closing of the eyelids that would relieve those symptoms and that induced by the neuromuscular spasm of BEB. Indeed, they generally expressed that it was a relief to no longer fight against the orbicularis spasm. Notably, the voluntary and prolonged closing of the eyelids alleviated the fighting of the sensory (irritation of the ocular surface secondary to DES) and motor nervous systems trying to control agonist–antagonist muscle phenomena (spasm closing the orbicularis muscles and voluntary contraction of the superior palpebral levator to keep the eyelids open).

That patients stated that their “ocular surface” discomfort was relieved by closing their eyes could explain the numerous and frequent misdiagnoses given these patients. The description of their symptoms during the examination by their general practitioner, usually the first doctor consulted, far from palpebral problem, disoriented the diagnosis towards an ocular surface pathology, i.e. DES. Therefore, artificial tears were prescribed with persistence of pain and orbicularis spasms. On average, our patients consulted as many as 8 practitioners, sometimes of different specialties, before being given a precise diagnosis and adapted therapy. The most frequently consulted specialists were ophthalmologists and neurologists, with general practitioners being the most common primary care physicians.

The exceptionally high frequency of DES observed in BEB up to 87% of patients in our study,

give this symptom a clue for BEB, and could help to reduce the delay for the diagnosis.

The impact on the quality of life of these patients during this period without a correct diagnosis, was very marked, as much on the physical level (pain, photophobia, DES) as on the psychological level; patients were considered by family members and some doctors to have a hysterical conversion disorder, and were sometimes, wrongfully, referred for psychiatric care. Only better recognition of the pathognomonic link that exists between DES and BEB, identifying DES as one of the key elements to the positive diagnosis of BEB, will achieve a more rapid diagnosis of BEB that remains poorly known and still under diagnosed.

When confronted with a patient complaining of frequent blinking and painful DES relieved by voluntary closing of the eyes, practitioners should keep in mind BEB diagnosis. Based on our 144 BEB patients, Schirmer-I test results showed an exceptionally strong correlation between the frequency and severity of DES and BEB, with respective scores of <15 for 86.8% and <10 mm for 76.3% of them. Moreover, bilateral and symmetrical DES appeared to be an integral part of the facial dystonia known as BEB, independent of sex, age or BEB severity grade as already noticed [17]. Instillation of artificial tears partially relieved the symptoms of DES but had no impact on BEB which responded only at quarterly injections of botulinum toxin A.

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Legend

Table 1. Grades of Blepharospasm Severity

Table 2. Description of 144 Patients with Benign Essential Blepharospasm (BEB)

Figure 1. Number of patients with BEB according to the value of Schirmer I test (mm).

Figure 2. Absence of correlation between Schirmer I-test score and age (years)

Table 1. Grades of Blepharospasm Severity

Grade	Symptoms
1	Occasional eyelid spasms that do not interfere with daily life
2	Spasms several times a day visible to others, incapable of prolonged looking at a screen (example: television)
3	Driving becomes impossible, hesitation in going out on one's own, reading becomes difficult, viewing a film becomes impossible
4	Total loss of autonomy, impossible to go out on one's own, read or look at a screen, frequent falls and loss of balance

Table 2.

Characteristic	Males	Females	All Patients
No. of subjects	34	110	144
Age, years			
At Schirmer test	66.8±13.2	68.7±11	68.3±11
At BEB onset	56±15	59±10.5	58.6±11.7
Months to diagnosis	52±117	40.5±48	43±69.5
Schirmer-test score			
Both eyes	7.1±9	5.4± 6	5.79±7.5
Right eye	5.6±8.6	5.9±7.6	5.8±7.8
Left eye	7.2±9.8	4.9±6.7	5.5±7.5
BEB intensity score, n (%)			
1	1 (3)	1 (0.9%)	2 (1.4)
2	11 (32.4)	19 (17.3%)	30 (20.8)
3	7 (20.6)	30 (27.3%)	37 (25.8)
4	15 (44.1)	60 (54.5%)	75 52.1)

Values are means±SD unless stated otherwise.

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Figure 1.

Figure 2.

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