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Diagnostic criteria for blepharospasm: A multicenter international study

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Abstract

Background: There are no widely accepted criteria to aid the physician in diagnosing BSP.

Objective: To validate recently proposed diagnostic criteria for blepharospasm in a larger and geographically diverse population and to develop a screening system for blepharospasm.

Methods: Video-recordings from 211 blepharospasm patients and 166 healthy/disease controls were examined by 8 raters. Agreement for presence of orbicularis oculi spasms, sensory trick, and

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increased blinking was measured by k statistics. Inability to voluntarily suppress the spasms was asked by the examiner but not captured in the video. Patients/controls were also requested to fill a self-administered questionnaire addressing relevant blepharospasm clinical aspects. The diagnosis at each site was the gold standard for sensitivity/specificity.

Results: All the study items yielded satisfactory inter/intra-observer agreement. Combination of items rather than each item alone reached satisfactory sensitivity/specificity. The combined algorithm started with recognition of spasms followed by sensory trick. In the absence of a sensory trick, including "increased blinking" or "inability to voluntarily suppress the spasms" or both items yielded 88–92% sensitivity and 79–83% specificity. No single question of the questionnaire yielded high sensitivity/specificity. Serial application of the questionnaire to our blepharospasm and control subjects and subsequent clinical examination of subjects screening positive by the validated diagnostic algorithms yielded 78–81% sensitivity and 83–91% specificity.

Conclusion: These results support the use of proposed diagnostic criteria in multi-ethnic, multi-center cohorts. We also propose a case-finding procedure to screen blepharospasm in a given population with less effort than would be required by examination of all subjects.

Keywords

Blepharospasm; Dystonia; Diagnosis

1. Introduction

Blepharospasm (BSP) is an adult-onset focal dystonia characterized by excessive contractions of orbicularis oculi (OO) and adjacent nearby facial muscles [1,2]. Involuntary contractions may spread to other body sites in approximately half of patients over 5 years [3–5]. Although there is no disease-modifying therapy, BSP may be effectively relieved by botulinum toxin (BoNT) or surgical treatments such as myectomy/neurectomy [1,6].

The diagnosis of BSP is based on clinical observation and is therefore error-prone. The main source of error are several conditions of involuntary eyelid closure, including tics, hemifacial spasm (HFS), facial chorea, apraxia of eyelid opening (AEO), and lid ptosis due to myasthenia or other causes) [7]. There are no widely accepted criteria to aid the physician in diagnosing BSP, even though several lines of evidence indicate that, in the absence of specific criteria, there is considerable variability in the diagnosis [8]. It would therefore be useful to develop tools allowing the early detection and surveillance of the disease.

A recent pilot study identified four clinical items (stereotyped, bilateral and synchronous orbicularis oculi spasm; sensory trick; increased blinking; and inability to voluntarily suppress the spasms) as diagnostically relevant for BSP [7]. A combination of such items yielded 93% sensitivity and 90% specificity in confirming or refuting suspected BSP. This guideline requires direct examination of subjects and is not practical for population surveys aiming at assessing frequency of and risk factors for BSP. The previous study was based on a relatively small sample of BSP patients (n. 30) and controls (n. 40), and all participants and evaluating physician were from the same country, Italy.

The present study was designed to validate recently proposed diagnostic criteria for BSP in a larger and geographically diverse population, to develop and validate a specific questionnaire to screen for BSP in a population, and lastly to explore the sensitivity/specificity of using the questionnaire followed by the proposed criteria for diagnosing BSP.

2. Subjects and methods

Data were acquired from the Dystonia Coalition (www.rarediseasesnetwork.org/dystonia/) project, “Diagnostic and Rating Tools for Blepharospasm”, a multicentre, observational study of people with isolated BSP. Participants were enrolled across 10 sites in the USA and Europe. Inclusion criteria for both case and control subjects were age 18 or more, any gender, any racial-ethnic background, and willingness and mental/physical ability to sign informed consent and participate in the protocol.

Patients needed to have isolated idiopathic BSP diagnosed by an experienced movement disorder neurologist. Exclusion criteria were secondary BSP [9], and co-existing medical conditions/surgical interventions that could confound assessments of BSP. Concomitant medication and BoNT treatment were allowed, but patients needed to be sufficiently symptomatic at recruitment to ensure that the clinical features were evident to evaluators. The last BoNT treatment session should have been performed at least 10 weeks prior to examination.

The control group included normal subjects or patients who had disorders involving the face and/or eyelid that could be confused with BSP (disease controls), including HFS, facial tics, facial chorea, AEO, lid ptosis due to myasthenia or other conditions, and psychogenic BSP.

2.1. Assessing accuracy of the proposed diagnostic guideline

Participants were video-recorded according to a standardized protocol that reproduced all the major/distinctive features identified by the clinical examination, including standard manoeuvres triggering eyelid spasms, demonstrating a sensory trick if present, and assessing blinking rate. Raters had a training session during which each type of abnormality was defined [7]. Spasm was defined as eyelid narrowing/closure associated with involvement of muscles beyond the eyelid, such as OO muscle. This evidence came specifically from a downward movement of the eyebrow or upward movement of the lower eyelid region. Duration was not considered, because it is possible to have a spasm <1 s. Sensory trick was defined as any kind of manoeuvre performed by the patient that led to a transient reduction in spasm severity in the period of time immediately after its execution [10,11]. Blink was defined as a short and brief eye closure involving eyelid only [2]. Blink rate per min was calculated with subjects at rest and eyes open during 2 min. Under this condition, any eyelid closure was considered a “blink”, and the cut off distinguishing normal and increased blinking was set at 16 blinks per min based on the earlier pilot study [7]. Subjects were also asked about their capability to voluntarily suppress the spasms defined as an inner volitional effort rather than voluntary compensatory frontalis muscle overactivity [7]. There was no duration requirement for voluntary suppression. Videotapes were reviewed after collection, the diagnosis of the patients was verified by G.D., and any concerns regarding the diagnosis

from the recruiting site were subsequently adjudicated by unanimous consensus of M.H., H.J., and J.P.

Inter-/intra-rater agreement was assessed among eight independent raters from the centers participating in the project. The number of videos included in the reliability study (106 video-recordings of 53 BSP patients and 53 control subjects) largely exceeded those based on the recommended subject-to-item ratios (that usually consider the assessment of 5–10 subjects for each item of a new scale) and on the number of items (n.4) contributing to diagnostic criteria. Items to be assessed were: (i) stereotyped, bilateral and synchronous OO spasms inducing narrowing/closure of the eyelids (item 1); (ii) effective sensory trick (item 2); (iii) increased blinking (item 3). The fourth clinical item ("inability to voluntarily suppress the spasms") was not included in the reliability analysis because the question about item 4 was asked by the site examiner but not captured in the video.

Since examination of 106 video-recordings from each rater would be excessively time-consuming, we adopted the following procedure to compare raters' judgement: (i) each rater had 40 randomly selected videos (20 from case patients and 20 from control subjects); (ii) raters did not rate videos from their own sites; and (iii) each video was rated by three different observers. By this approach, each rater was compared with all other raters on 40 videos, though each other rater scored only 8 to 14 of the videos examined by the first rater. For intra-rater assessment, each rater was asked to re-evaluate five videos, at least two weeks following the first rating. Raters could not see their prior ratings.

Agreement among raters was assessed by k index that measures the level of agreement beyond chance and ranges from −1 (perfect disagreement) to +1 (perfect agreement). K index >0.4 (indicating moderate to substantial/almost perfect agreement) was considered to be satisfactory [12].

To assess sensitivity and specificity of each item, or combination of items, the gold standard was the diagnosis made at each site by the senior neurologist, and verified as noted earlier. Sensitivity was defined as the proportion of subjects who screened positive among those who were given a diagnosis of BSP on clinical examination (true positives/true positives + false negatives). Specificity was the proportion of subjects who screened negative among those who were judged as non BSP on clinical examination (true negatives/false positives + true negatives).

2.2. Assessing accuracy of a BSP screening questionnaire

BSP patients and controls were requested to complete a self-administered questionnaire, the BSP screening questionnaire (BSQ). The questionnaire consisted of 10 questions formulated by a panel of four experts (MH, HJ, AB and GD) that addressed the relevant clinical aspects of BSP (Table 3). Participants were only instructed to answer each question yes or no. In the case of illiterate individuals, a proxy relative was asked to read them the questionnaire without any comments. Sensitivity and specificity of each question, and of combination of questions, was assessed. The gold standard was the diagnosis made at each center by the senior neurologist.

2.3. Simulation of a multistep procedure to diagnose BSP in a population

We simulated a case finding-procedure based on serial application of the BSQ and the validated diagnostic algorithms. We first selected all patients and controls answering yes to one or more of the questions reaching higher specificity as defined in the previous step. Thereafter, the validated clinical diagnostic algorithm was applied to subjects screening positive to identify individuals affected by BSP. Finally, sensitivity/specificity values and percent of subjects undergoing clinical examination was calculated.

2.4. Standard protocol approvals, registrations, and Patient Consents

The study was approved by the ethical committee from all participating sites. Written informed consent was obtained from all participants. A signed Patient Consent-to-Disclose Form was obtained for videos of any recognizable patient.

3. Results

3.1. Validation sample

This included 211 patients with idiopathic BSP (age at onset, 53.3 ± 9.5 years) and 166 control subjects. Focal BSP was detected in 80 patients, BSP as part of a segmental/multifocal dystonia in 131 patients. Sensory trick was found in 123/211 patients (58%), increased blinking in 180/211 (85%), and inability to voluntary suppress the spasm in 184/211 (87%). The control group included: 53 normal subjects, 53 patients with HFS, 43 with tics, 6 with myasthenia, 6 with neuropathic lid ptosis, 3 with Bell's palsy, and 2 with psychogenic BSP. Case and control subjects were similar for sex distribution (65 men and 146 women vs. 61 men and 105 women, $p = 0.22$) but significantly differed for age (63.8 ± 8.8 vs. 51.1 ± 20.1, $p < 0.001$), which was mainly due to subjects recruited with tics. In the control group, 4 tic patients and 6 HFS patients reported touching the eyelids or the face as sensory trick.

3.2. Validation of the diagnostic guideline

Table 1 shows that inter-rater agreement for item 1 was substantial to almost perfect in seven combination of raters, moderate in only one combination; substantial to almost perfect inter-rater agreement was reached in all combination of raters for both items 2 and 3. Intra-rater agreement yielded k values ranging between 0.54 (moderate agreement) to 1 (perfect agreement).

No study item alone reached satisfactory combination of sensitivity/specificity: item 1 reached the greatest sensitivity and item 2 the greatest specificity (Table 2). Therefore, we tested whether algorithm resulting from combination of items (Table 2) would improve diagnostic sensitivity/specificity.

The combined algorithm started with item 1 followed by recognition of item 2, "sensory trick". In the absence of a sensory trick, including item 3 "increased blinking" (algorithm 123) yielded 90% sensitivity and 82% specificity. Similar values were obtained by the algorithm 124 that included item 4, "inability to voluntarily suppress the spasms" (88%

sensitivity and 83% specificity). Including both items 3 and 4 (algorithm 1234) yielded 92% sensitivity and 79% specificity.

In algorithm 123, false positives included 0/53 normal subjects, 27/43 tic patients (64%), 1/56 patients with HFS/Bell's palsy (4%), 0/12 patients with ptosis due to myasthenia/neuropathy, and 1/2 patients with psychogenic BSP. In algorithm 124, false positives included 0/53 normal subjects, 23/43 tic patients (47%), 3/56 patients with HFS/Bell's palsy (5%), 1/12 patients (8%) with ptosis due to myasthenia/neuropathy, and 1/2 patients with psychogenic BSP. In algorithm 1234, false positives included 0/53 normal subjects, 30/43 tic patients (70%), 3/56 patients with HFS/Bell's palsy (5%), 1/12 patients with ptosis due to myasthenia/neuropathy (8%), and 1/2 patients with psychogenic BSP.

3.3. Sensitivity and specificity of the BSP screening questionnaire

No single BSQ question yielded high sensitivity/specificity (Table 3). However, questions 1 and 10 yielded sensitivity >80% while the best specificity (76–78%) was reached by questions 3, 5, and 6. Stratifying control group by disease controls and normal subjects (Table 3), no questions could distinguish BSP patients from disease controls with specificity >67%, whereas questions 1 to 6 and question 10 distinguished BSP patients from normal controls with >95% specificity. We found no significant differences in sensitivity and specificity associated with age, sex, and years of schooling (data not shown).

3.4. Simulation of a multistep procedure to diagnose BSP in a population

Simulation (Fig. 1) started with self-administration of the BSQ to the 377 subjects participating into the study (211 BSP patients and 166 controls). We then selected all subjects answering yes to one or more of the three questions reaching highest specificity (questions 3, 5 and 6). This excluded 127 subjects (32 BSP patients, 49 normal controls and 46 disease controls) who were not further examined. In the remaining 250 subjects, the algorithm 123 identified 165 BSP patients and 15 controls as affected by BSP; the algorithm 124 identified 164 BSP patients and 15 controls as affected by BSP; and the algorithm 1234 identified 170 BSP patients and 18 controls as affected by BSP. Overall, the case-finding procedures yielded 78–81% sensitivity and 83–91% specificity by clinically examining 250/377 subjects (66%).

4. Discussion

4.1. Diagnostic guideline

Under our validation procedure, items 1 to 3 reached satisfactory inter-rater agreement, with most combination of raters yielding substantial to almost perfect agreement [12]. Item 4 was not considered for reliability analysis because it was assessed by a patient's answer to a standardized question. With regard to diagnostic accuracy, item 1 (stereotyped, bilateral and synchronous OO muscle spasms inducing eyelid narrowing closure) could differentiate BSP from facial chorea (non-stereotyped movements), HFS (contractions were usually unilateral), AEO (not spasm), and lid ptosis due to myasthenia or other causes (not spasm). Item 1 reached the greatest sensitivity (96%), thus suggesting that it is crucial for diagnosing BSP, but yielded only 76% specificity, indicating a high risk of misclassifying

several BSP cases. Sensory trick (item 2) was associated with the greatest specificity (92%). Among controls, 4 tic patients and 6 HFS patients reported a sensory trick (touching the eyelid or the face). In tic patients we could not be sure that this was a true trick rather than the result of voluntary spasm suppression characterizing tics. Likewise, patients with HFS may sometimes display spam improvement with tactile stimulation, even though it could represent mere alleviation of the spasm due to local compression of the muscle [14]. With regard to item 3 (increased blinking), its moderate sensitivity may depend, at least in part, on long OO spasms that decrease (mask) blink rate; whereas the low specificity associated with item 3 is probably related to the significant amount of variability in blink rate among normal subjects due to the psychological status. The low specificity yielded by item 4 ("inability to voluntarily suppress the spasms") probably reflected variability caused by the patients' education, test circumstances and attitude of the observer. Although no study item alone allowed an accurate diagnosis of BSP, combining the four items yielded three diagnostic algorithms (Table 2) that were sensitive and specific enough. The 88–92% sensitivity and 79–83% specificity reached by these algorithms means that they can correctly diagnose BSP in about 9/10 patients who have the condition; and can correctly identify as not having BSP about 8/10 subjects who do not have the condition. Considering that the frequency of sensory trick may be even higher (up to 71%) than in our BSP sample [13], particularly in patients with short disease duration [10], then diagnostic accuracy might increase in newly diagnosed patients.

Although the three algorithms showed similar specificity, they differed for the frequency of the subjects with tics who yielded false-positive results. Algorithm 124 could better identify tic patients as not having BSP than algorithms 123 and 1234. However, the latter algorithms showed a slightly higher sensitivity. The choice of the algorithm to be used may depend on the patient population attending the site, and on the possibility to reliably assess increased blinking and capability to voluntarily suppress the spasms.

4.2. BSP screening questionnaire

Although screening tools have been proposed for cervical dystonia [15] and adult-onset dystonia overall [16], this is the first attempt to design and validate a questionnaire to specifically screen BSP. The 10 questions contained in the BSQ yielded 52–85% sensitivity and 59–78% specificity. The unsatisfactory specificity values were mainly due to disease controls, whereas the comparison of BSP patients with normal controls yielded very high specificity (>95%) for most questions. Overall, this validity study might have been limited by the clinic-based sample and by the fact that our basic questions were related to BSP phenomenology but not to possible misdiagnosis (e.g., local pain, weakness, paresthesia). Asking such questions, however, might have likely increased specificity and further decreased sensitivity. Regardless of the explanation, the low diagnostic accuracy of the BSQ and the high inter-rater agreement (with high sensitivity and specificity) yielded by examiners when assessing BSP indicate that, at present, there is no replacement of a direct examination for diagnosing BSP.

4.3. Simulation of a multistep procedure to diagnose BSP in a population

The aforementioned considerations suggest that BSQ alone cannot be used as a tool to screen BSP in population-based groups. Nevertheless, it might be a screening resource to be used in the context of a more complex procedure (Fig. 1).

The first step of our simulation (selection of subjects answering yes to one or more of the three BSQ questions reaching higher specificity) resulted in the exclusion of 127 subjects (32 cases and 95 controls) who were not further examined. By clinically examining the remaining 250/377 subjects (66%), diagnostic algorithms provided sensitivity and specificity values that were relatively high but not fully acceptable.

4.4. Conclusions

This study has several strengths. First, it was performed in a large population and included participants and physician from several countries and languages. Second, the BSP population was representative of the general population of cases in terms of demographic/clinical features [1]. Third, most conditions mimicking BSP were included in the control group with a frequency distribution that resembled their real-world relative frequency [17–21]. The relatively less specificity to distinguish tics from BSP may be disappointing but understandable [16]. Fourth, video-recording protocol included examination of all body sites during several tasks, allowing manifestation and detection of OO spasms under several conditions. Finally, the standard for comparison was represented by dystonia status based on clinical examination by expert neurologists and achieved satisfactory diagnostic reliability.

In conclusion, the sensitivity and specificity values reached by the diagnostic algorithms in our validation setting strongly support the use of this clinical tool in multi-center cohorts. We also propose a case-finding procedure based on serial application of a self-administered questionnaire and examination of subjects screening positive by the validated diagnostic algorithms. Although such a procedure did not yield high sensitivity, it may nevertheless be a good “first step” to develop a screening protocol that helps to identify BSP patients in a given population at a consistently lower cost and with less effort than would be required by examination of all subjects.

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The study was approved by the ethical committee from all participating sites. Written informed consent was obtained from all participants. A signed Patient Consent-to-Disclose Form was obtained for videos of any recognizable patient. Any data not published within the article is available in a public repository and include digital object identifiers or accession numbers to the datasets. Anonymized data will be shared by request from any qualified investigator.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. All authors have participated to the conception of the study, to the analysis of data and to the article preparation. All authors have approved the final article.

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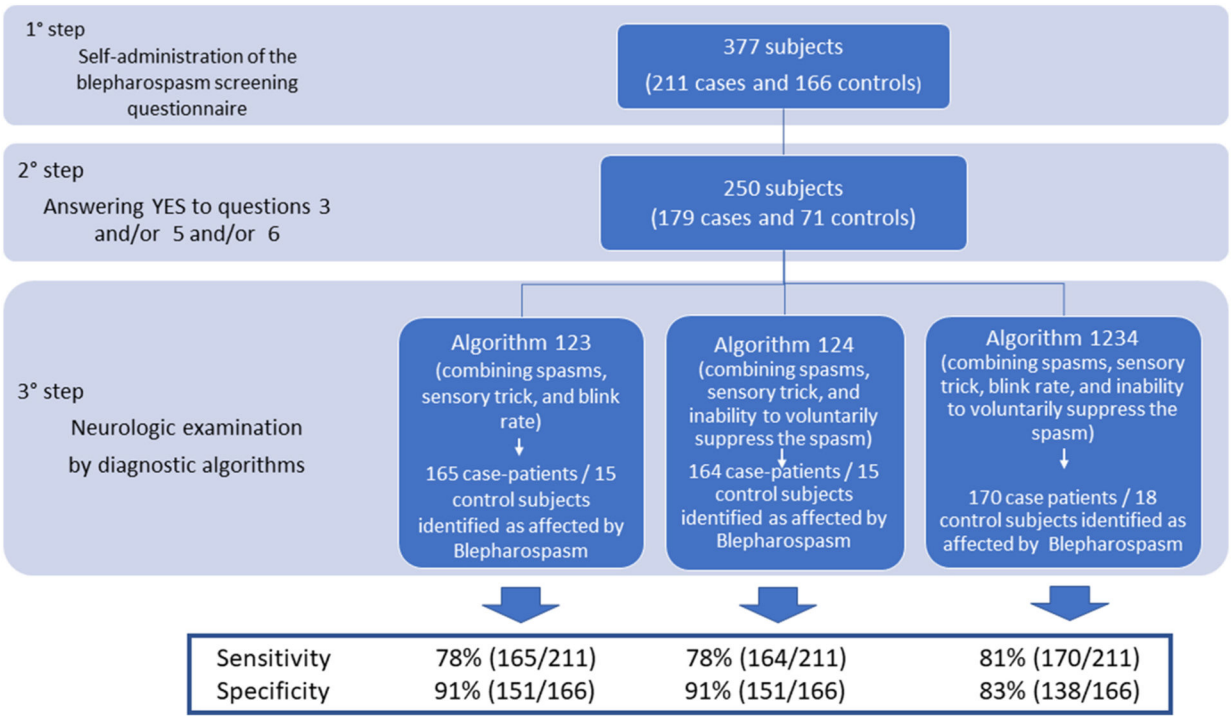

Fig. 1.
Multistep blepharospasm-finding procedure in a group-based sample.

Table 1

Inter-observer agreement (k statistics) on diagnostic item 1 (stereotyped, bilateral and synchronous orbicularis oculi spasms inducing narrowing/closure of the eyelids), item 2 (effective sensory trick), and item 3 (increased blinking [greater than or equal to 16 blinks/min with subject at rest with eyes open]).

Raters	Item 1K index (p value)	Item 2K index (p value)	Item 3K index (p value)
Rater 1 vs all other raters	0.74 (<0.00001)	0.87 (<0.00001)	0.80 (<0.00001)
Rater 2 vs all other raters	0.85 (<0.00001)	0.72 (<0.00001)	0.93 (<0.00001)
Rater 3 vs all other raters	0.61 (0.0001)	0.64 (<0.00001)	0.83 (<0.00001)
Rater 4 vs all other raters	0.69 (<0.00001)	0.80 (<0.00001)	0.93 (<0.00001)
Rater 5 vs all other raters	0.56(<0.00001)	0.70 (<0.00001)	0.79 (<0.00001)
Rater 6 vs all other raters	0.75 (<0.00001)	0.75 (<0.00001)	0.74 (<0.00001)
Rater 7 vs all other raters	0.83 (<0.00001)	0.69 (<0.00001)	0.82 (<0.00001)
Rater 8 vs all other raters	0.80 (<0.00001)	0.79 (<0.00001)	0.89 (<0.00001)

Table 2

Sensitivity and specificity of clinical diagnostic items 1 to 4 and of combination of items.

Clinical item	Case patients (n. 211) identified as affected by blepharospasm	Control subjects (n. 166) identified as affected by blepharospasm	Sensitivity/specificity
1. Presence of stereotyped, bilateral and synchronous orbicularis oculi spasm	200	37	95%/78%
2. Presence of effective sensory trick	123	10	58%/94%
3. Increased blinking	180	83	85%/50%
4. Inability to voluntarily suppress the spasms	184	81	87%/52%
Combination of items (algorithm)			
Items [1 + 2] (algorithm 12)	119	4	56%/98%
Items [1 + 3] (algorithm 13)	174	28	82%/84%
1Items [1 + 4] (algorithm 14)	178	27	84%/84%
Items [1 + (2 or 3)] (algorithm 123)	190	29	90%/82%
Items [1 + (2 or 4)] (algorithm 124)	185	28	88%/83%
Items [1 + (2 or 3 or 4)] (algorithm 1234)	195	35	92%/79%

Table 3

Questions included in the Blepharospasm Screening Questionnaire. Sensitivity and specificity of each question was tested in 211 blepharospasm patients and 166 control subjects (52 normal controls and 114 disease controls).

Questions	N. blepharospasm patients answering yes (Sensitivity)	N. control subjects answering yes (Specificity)	N. normal control subjects answering yes (Specificity)	N. of disease control patients answering yes (Specificity)
1. Do you find your eyes closing against your will?	179 (85%)	64 (61%)	1 (98%)	63 (45%)
2. Do you find your eyelids fluttering against your will?	154 (73%)	72 (57%)	2 (96%)	70 (39%)
3. Do you have trouble seeing because your eyes are closed?	149 (71%)	40 (76%)	2 (96%)	38 (58%)
4. Have other people told you that you close your eyes or blink too much?	135 (64%)	51 (69%)	1 (98%)	50 (56%)
5. Have other people told you that your eyes are sometimes not fully open?	109 (52%)	38 (77%)	1 (98%)	37 (67%)
6. Does touching your face help to open your eyes when they close against your will?	127 (60%)	37 (78%)	0 (100%)	37 (67%)
7. Do your eyes ever feel dry?	156 (74%)	75 (55%)	17 (67%)	58 (49%)
8. Do you have any gritty, sandy or burning sensation in your eyes?	139 (66%)	46 (72%)	7 (86%)	394 (66%)
9. Do you find bright lights to be particularly unpleasant or to cause your eyes to close?	160 (76%)	57 (66%)	8 (85%)	49 (57%)
10. Did you ever see a doctor about excessive blinking or closing of your eyes?	173 (82%)	67 (60%)	0 (100%)	67 (41%)