Is increased blinking a form of blepharospasm?

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ABSTRACT

Objective: The aim of this study was to investigate whether increased blink rate (BR) is part of the clinical spectrum of primary blepharospasm (BSP).

Methods: We enrolled 40 patients (16 patients with an increased BR but without typical orbicularis oculi [OO] spasms, and 24 patients with typical involuntary OO spasms) and 18 healthy subjects. The BR, blink reflex recovery cycle, and somatosensory temporal discrimination threshold (STDT) were tested in patients and controls.

Results: Patients who had typical OO spasms had an altered R2 recovery cycle whereas those who had an increased BR alone had a normal blink reflex recovery cycle. STDT values were higher in patients than in healthy subjects and no difference was found in the STDT abnormalities in the 2 groups of patients.

Conclusions: Our study shows that, despite the similar STDT abnormalities, the different changes in the R2 recovery cycle in patients with BSP and those with increased BR alone suggest that these disorders arise from different pathologic mechanisms. *Neurology*® 2013;80:2236–2241

GLOSSARY

ANOVA = analysis of variance; **BR** = blink rate; **BSP** = blepharospasm; **ISI** = interstimulus interval; **OO** = orbicularis oculi; **STDT** = somatosensory temporal discrimination threshold.

Patients who present with excessive involuntary eyelid closure raise a diagnostic challenge. Whereas some patients have sustained orbicularis oculi (OO) spasms and are therefore diagnosed as having blepharospasm (BSP), a common focal dystonia,[1–4] others have increased blinking alone. In these patients, increased blinking may reflect ophthalmologic disorders involving the ocular surface, tear film, or eyelids but can manifest also in apparently healthy subjects without any secondary causes.[5] Although increased blinking at rest and during conversation may occur in patients with BSP,[6] and some suggest that increased blinking is sometimes a prodromal sign of primary BSP,[2] no evidence yet shows whether patients with increased blinking alone have a dystonia subtype, essentially a forme fruste of BSP.

Our aim in this case-control study was to investigate whether increased blinking is a subtype of primary BSP. To do so, we tested the blink rate (BR) and the neurophysiologic variables known to be altered in primary BSP, the blink reflex recovery cycle—reflecting brainstem excitability[7–10]—and somatosensory temporal discrimination threshold (STDT),[11–13] in patients presenting with excessive involuntary eyelid closure who had sustained OO spasms (primary BSP), those with increased blinking alone, and healthy age-matched control subjects.

METHODS

Study participants. Among consecutive patients with excessive involuntary eyelid closure who were seen in our movement disorders outpatient clinic, we identified 16 subjects with increased blinking without sustained OO spasms. These subjects could not voluntarily control the excessive blinking and reported no premonitory sensation before eyelid movements. Nor did any evidence suggest a psychogenic movement disorder such as persisting unilateral or asymmetric symptoms, paroxysmal symptoms, and other inconsistencies such as pain, associated somatizations, blinking diminished by distraction, unusual sensory tricks, or unexpected response to botulinum toxin injections. We also recruited 24 consecutive patients with primary BSP (either focal or related to segmental dystonia) diagnosed in accordance with published criteria[14] and 18 healthy control subjects. Exclusion criteria for all study subjects were the

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presence of other eyelid abnormalities (such as apraxia of eyelid opening, and other disorders including tics or tardive syndromes) in addition to involuntary eyelid closure due to BSP or excessive eye blinking alone; history of exposure to dopamine receptor blocking agents within 6 months before the onset of involuntary eyelid closure; features suggesting secondary causes of involuntary eyelid closure; presence of neuropathy and Mini-Mental State Examination score <26 (for the STDT examination); and prior ophthalmologic disorders or use of contact lenses.

Increased blinking as well as BSP was diagnosed by a movement disorders specialist (A.B.). All subjects had stopped taking drugs that would potentially act on the CNS for at least 24 hours before the study, and those receiving botulinum toxin had the last injection at least 4 months before the study.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all patients and healthy subjects, and the experimental procedure was approved by the institutional review board at Sapienza University of Rome, and conducted in accordance with the Declaration of Helsinki.

Clinical assessment. Information regarding demographic features, medical and family history, disease course, and treatment were collected during a face-to-face interview. All patients were clinically evaluated by using the Jankovic Rating Scale[15] (patients with BSP: 5.56 ± 0.3; patients with increased BR: 3.2 ± 0.2). All study subjects were video-recorded while undergoing a standard clinical examination. Each video segment lasted long enough to reproduce all the major features in the clinical examination and was integrated with standard maneuvers triggering facial spasms and possibly revealing causes of eyelid closure other than BSP or excessive blinking. The senior neurologist (A.B.) reviewed the video recordings to check for sustained involuntary OO spasms and calculate the BR. The BR was calculated with subjects at rest and eyes open during the final video segment (lasting about 150 seconds) and was expressed as blinks per minute. Blink was defined as a transient, bilateral, and synchronous short-duration (<1 second) eyelid drop unassociated with lowering of the eyebrows beneath the superior orbital margin.[6,16,17] Two blinks were considered as separate if they could be separated visually from each other. A sudden, involuntary, long-lasting OO muscle contraction causing bilateral eyelid narrowing/closure was classified as a muscle spasm.[1,14] A brief eyelid closure with the eyebrow beneath the superior orbital margin was considered a brief spasm.

All participating subjects were also screened for ophthalmologic complaints with a previously validated questionnaire that yielded 76.5% sensitivity and 94.1% specificity in identifying complaints referred to diseases involving the anterior segment of the eye.[18]

Blink reflex recovery cycle. The blink reflex recovery cycle was studied, according to the experimental procedure reported in previous studies, by delivering electrical shocks to the supraorbital nerve through silver chloride disc surface electrodes.[1,8] The cathode was placed over the supraorbital foramen and the anode 2 cm above. For electrical stimulation, we used square-wave pulses with a pulse width of 200 microseconds. The R2 threshold was determined as the minimum intensity required to evoke a reliable R2 response with an amplitude of at least 50 μV. Stimulus intensity was set at 2 times the threshold to evoke a consistent R2 response (2 TR2). Paired electrical stimuli were given at interstimulus intervals (ISIs) of 250, 500, and 1,000 milliseconds. Twenty trials for single- and paired-pulse (250-, 500-, and 1,000-millisecond ISIs) were performed with an intertrial interval of about 40 to 60 seconds.[1,19] EMG responses were recorded with pairs of silver chloride disc surface electrodes placed over both OO muscles. Trials with movement artifacts were rejected. The EMG signal was amplified and bandpass filtered (20 Hz to 3 kHz). The R2 response area was calculated for each block with Signal software. The onset and offset for the R2 response were estimated visually from averaged rectified EMG measures. We also calculated the R2 recovery index (mean percentage R2 area inhibition at 250- and 500-millisecond ISIs).[10,20,21]

Somatosensory temporal discrimination threshold. STDT was investigated by delivering paired stimuli starting with a 0-millisecond ISI (simultaneous pair), and progressively increasing the ISIs (in 10-millisecond steps) according to the experimental procedures already used in previous studies.[12,13,22–24] Paired tactile stimuli consisted of square-wave electrical pulses delivered with a constant-current stimulator (Digitimer DS7AH; Digitimer Ltd., Hertfordshire, UK) through surface skin electrodes on the right index finger with the anode located 0.5 cm distally from the cathode. The stimulation intensity was defined for each subject by delivering a series of stimuli at increasing intensity from 2 mA in 1-mA steps; the intensity used for STDT was the minimal intensity perceived by the subject in 10 of 10 consecutive stimuli. Before starting STDT testing, subjects familiarized themselves with the task and achieved a stable performance. Subjects were asked to report whether they perceived a single stimulus or 2 temporally separated stimuli by saying "one" or "two" after each stimulation. The first of 3 consecutive ISIs at which participants recognized the stimuli as temporally separated was considered the STDT. To keep subjects' attention level constant during the test and to minimize the risk of perseverative responses, the STDT testing procedure included "catch" trials consisting of a single stimulus randomly delivered. Each session comprised 4 separate blocks. The STDT was defined as the average of 4 STDT values, 1 for each block, and was entered in the data analysis.

The blink reflex recovery cycle and STDT were tested by neurophysiologists who were blinded to the clinical assessment and the patient group assignment (BSP or increased blinking alone).

Statistical analysis. Between-group (prolonged OO spasms vs increased blinking vs healthy subjects) repeated-measures analysis of variance (ANOVA) with factor ISI (250, 500, and 1,000 milliseconds) as main factor was used to analyze blink reflex recovery cycles (R2 component area) in the 2 groups of patients and healthy subjects. Between-group ANOVA was used to compare STDT values in patients and healthy subjects. Tukey honestly significant difference was used for post hoc analysis.

Spearman rank correlation was used to test possible correlations between demographic features (age and disease duration) and neurophysiologic abnormalities (BR, R2 recovery index, STDT values). Holm correction for multiple comparisons was used to disclose false significance. All values are expressed as means ± SE. A p value <0.05 was considered to indicate statistical significance.

RESULTS

Demographic and clinical features. The 24 patients with BSP, the 16 patients with increased blinking alone without sustained OO spasms, and the 18 healthy control subjects were similar for age (71 ± 2 vs 69 ± 3 vs 69 ± 2 years, $p = 0.69$), sex (12 men/12 women vs 8 men/8 women vs 8 men/10 women), disease duration (15 ± 2 vs 13 ± 2 years, $p = 0.37$), and ocular complaints (18/24 vs 11/16, $p = 0.51$).

Between-group ANOVA showed that BR differed in the 3 groups ($F = 29.65$, $p < 0.000001$). Post hoc analysis showed that patients with sustained OO

spasms and those who had increased blinking alone had a higher BR than healthy subjects (sustained spasms vs healthy subjects: $p = 0.003$; increased blinking vs healthy subjects: $p < 0.00005$) (figure 1).

Blink reflex recovery cycle. Between-group repeated-measures ANOVA showed a significant factor ISI ($F = 211.02$, $p < 0.0000002$) and group ($F = 76.98$, $p < 0.00001$), and a significant interaction of group and ISI ($F = 19.09$, $p < 0.000005$). Post hoc analysis showed that patients with sustained OO spasms had an altered blink reflex recovery cycle compared with healthy subjects ($p < 0.0001$), whereas those who had increased blinking alone had a blink reflex recovery cycle similar to that obtained in healthy subjects ($p = 0.144$) (figure 2).

Somatosensory temporal discrimination threshold. Between-group ANOVA for STDT values in healthy subjects and in the 2 groups of patients showed a significant effect of factor group ($F = 26.01$, $p < 0.000001$). Post hoc analysis showed that STDT values differed between patients and healthy subjects (healthy subjects vs patients with sustained OO spasms: $p < 0.0003$; healthy subjects vs patients with increased blinking: $p < 0.0001$), whereas they were similar in the 2 groups of patients (patients with sustained OO spasms vs patients with increased blinking: $p = 0.91$) (figure 3).

Spearman rank correlation showed that age and disease duration (Spearman $\rho = 0.56$, $p = 0.0001$) and BR and R2 recovery index (Spearman $\rho = -0.47$, $p = 0.002$) correlate.

DISCUSSION The present study confirms that the R2 blink reflex recovery cycle, the variable measuring brainstem interneuron excitability, is enhanced in patients with primary BSP defined traditionally as the presence of spasms. Conversely, a new finding is that this blink reflex variable is normal in patients who have increased blinking alone without sustained spasms. In the overall population of patients with excessive involuntary eyelid closure, we also found that the R2 recovery index and BR correlate, suggesting that when the BR is increased, brainstem interneuron excitability of the blink reflex circuit is normal. Finally, all the patients with involuntary eyelid closure had abnormally increased STDT values and no difference was found in the STDT alterations according to the presence or absence of sustained OO spasms.

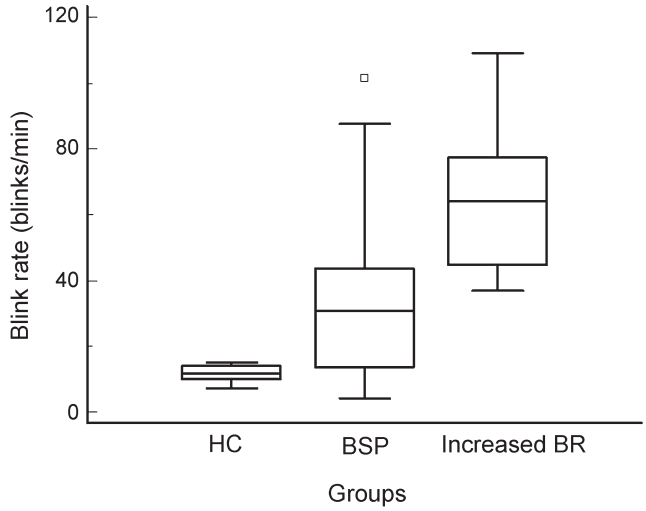
We took numerous precautions to obtain reliable data. For the BR measurements, because the mean BR depends on the length of data collection, patients and controls underwent exactly the same study protocol for video recording. For STDT testing, by using "catch trials," we constantly checked attention levels.[12] Because answers to the questionnaire on ocular symptoms showed similar frequencies in the 2 groups of patients, we can also reasonably exclude the possibility that increased blinking depends on ocular symptoms. The uncontrollable blinking with absence of urge in our patients with increased blinking makes it unlikely that these patients have tics.

The normal R2 recovery cycle in patients with increased blinking without sustained OO spasms is a new finding that appears to be in opposition to current knowledge on BSP. Previous studies have consistently reported an increased R2 recovery cycle in patients with BSP[8,9,21,25] and even in patients with cervical dystonia but without BSP.[26,27] This abnormality probably reflects the lack of inhibitory drive from the basal ganglia upon the pontomedullary circuits responsible for the blink reflex.[1,9,28] These patients all had overt spasms.

All of the patients we studied presented with increased spontaneous blinking. Spontaneous blinking appears to arise from an endogenous blink generator modulated by corneal afferents, dopamine, and cognitive states.[29] Evidence from a recent study in rats suggests that the spinal trigeminal complex is an integral component in the spontaneous blink generator circuit. The spontaneous blink generator circuit is under basal ganglia control.[30–32]

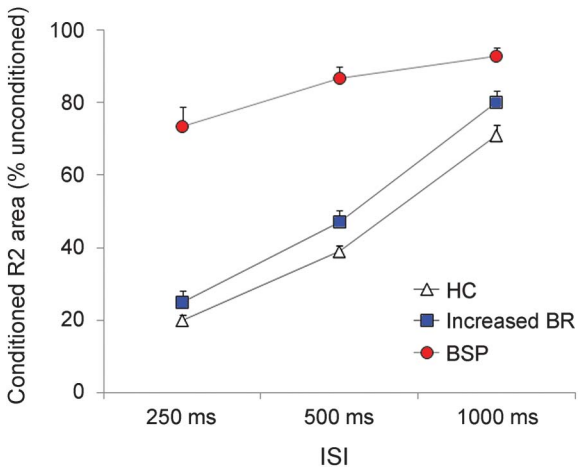
Our hypothesis is that in patients who manifest increased spontaneous blinking, the spontaneous blink generators are overactive. Overactivation can explain why patients in whom blinking is increased have apparent normal blink reflex circuitry excitability. If brainstem motoneurons and interneurons subserving the blink reflex fire at a high frequency, the second stimulus in the R2 recovery cycle would be less likely to activate them, thus resulting in a normal

Figure 1 Comparison of blink rate values in patients and healthy subjects



Blink rate (BR) in healthy control (HC) subjects, patients with blepharospasm (BSP), and patients with increased BR. On the y-axis, BR is expressed as number of blinks per minute.

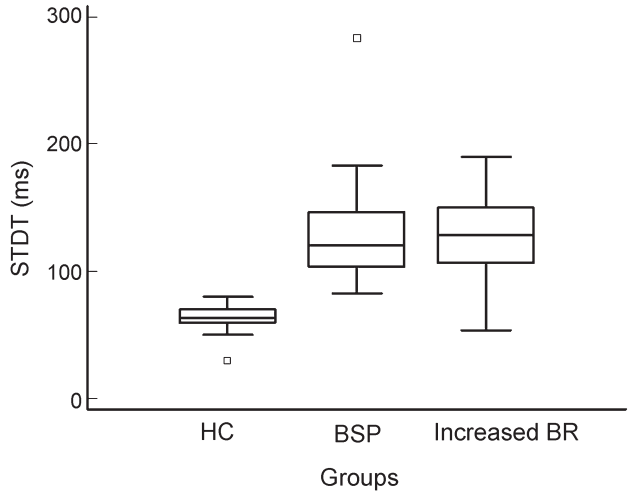
Figure 2 Comparison of the blink reflex recovery cycle in patients and healthy subjects



Blink reflex recovery cycle in healthy control (HC) subjects, patients with blepharospasm (BSP), and patients with increased blink rate (BR). On the y-axis, conditioned R2 response area is expressed as percentage of the unconditioned R2 response area. On the x-axis, interstimulus intervals (ISIs) are expressed in milliseconds.

R2 recovery cycle. Alternatively, assuming that the spontaneous blink generator is separate from the blink reflex circuit, and that both have to communicate with the OO motoneurons, we might suggest that increased blinking is not due to hyperexcitability of the OO motoneurons themselves. Whether spontaneous blink generator overactivation depends on altered descending control from basal ganglia or on altered projections from mesial frontal areas to basal nuclei remains unclear. The normal blink reflex recovery cycle (a variable known to be abnormal in several basal ganglia diseases)[16,33] argues against a basal ganglia dysfunction. Consistent with the observation that in patients with movement disorders low dopamine levels determine a reduced BR and enhanced R2 recovery index,[33] the correlation between BR and R2 recovery index further supports the hypothesis that the brainstem neural circuits for the BR differ from those for the R2 recovery cycle.

Figure 3 Comparison of the somatosensory temporal discrimination threshold in healthy control (HC) subjects, patients with blepharospasm (BSP), and patients with increased blink rate (BR)



On the y-axis, somatosensory temporal discrimination threshold (STDT) is expressed in absolute values (milliseconds).

The other new finding in our study is that patients with BSP and those with increased blinking alone share an abnormal STDT. The similar disease duration in our patients with BSP and increased BR might argue against the possibility that increased blinking will subsequently lead to OO spasms. Although STDT abnormalities are not specific for dystonia[24,34–36] and do not separate the patient groups, STDT testing does separate the blinkers from normal subjects. The similar abnormalities in STDT values in the 2 patient groups may well be a feature indicating continuity from increased blinking to spasm. Their increased blinking could lead to spasms similarly to how increased writing in predisposed patients leads to writer's cramp.

The normal recovery cycle we found in patients with excessive blinking resembles the normal blink reflex recovery cycle found in patients with psychogenic BSP[21] and the STDT abnormalities reported in psychogenic dystonia.[37] Despite these similarities, our patients who had involuntary excessive blinking alone had no clinical features indicating a psychogenic movement disorder.

Even though prior ophthalmologic disorders or use of contact lenses were excluded before study entry, the lack of a standardized ophthalmologic assessment might be acknowledged as a limitation of the study.

Our study shows that an altered R2 recovery cycle is associated with the presence of sustained involuntary OO spasms but not with increased blinking, whereas patients with primary BSP and patients with increased blinking share common STDT alterations. Despite the similar STDT abnormalities, the different changes in the R2 recovery cycle in patients with BSP and frequent blinking alone suggest that these disorders arise from different pathologic mechanisms. Whether patients with increased blinking alone and without prolonged OO muscle spasms are actually predisposed to BSP remains an open question for future research.

AUTHOR CONTRIBUTIONS

A. Conte: design of the study, analysis of the data, drafting the manuscript. G. Defazio: design of the study, revising the manuscript. G. Ferrazzano: analysis of the data. M. Hallett: revising the manuscript. A. Macerollo: analysis of the data. G. Fabbrini: interpretation of the data. A. Berardelli: design of the study, revising the manuscript.

STUDY FUNDING

This study was supported by the Benign Essential Blepharospasm Research Foundation.

DISCLOSURE

A. Conte, G. Defazio, and G. Ferrazzano report no disclosures. M. Hallett serves as Chair of the Medical Advisory Board for and receives honoraria and funding for travel from the Neurotoxin Institute. He may accrue revenue on US patent 6,780,413 B2 (issued August 24, 2004): immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US patent 7,407,478 (issued August 5, 2008): coil for magnetic stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. Dr. Hallett's research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds came from Ariston Pharmaceutical Company via a Cooperative Research and Development Agreement with NIH for treatment studies of essential tremor, and the Kinetics Foundation, for studies of instrumental methods to monitor Parkinson disease, BCN Peptides, S.A., for treatment studies of blepharospasm, and Medtronics, Inc., for studies of deep brain stimulation, via Clinical Trials Agreements with NIH. A. Macerollo reports no disclosures. G. Fabbrini received research support from Allergan, Lundbeck, and Novartis. A. Berardelli received research support from Allergan, Lundbeck, and Merz. Go to Neurology.org for full disclosures.

Received November 26, 2012. Accepted in final form March 7, 2013.

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