Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Increased Blinking May Be a Precursor of Blepharospasm: A Longitudinal Study

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Abstract: **Background:** The objective of this 5-year longitudinal study was to investigate whether patients with increased blinking develop orbicularis oculi muscle spasms.
Methods: Eleven patients who initially manifested increased blinking alone were clinically and neurophysiologically re-evaluated 5 years later.
Results: By the 5-year follow-up assessment, 9 of the 11 patients had developed orbicularis oculi muscle spasms. The blink reflex recovery cycle became abnormal, whereas somatosensory temporal discrimination, which already was abnormal at the first evaluation, did not significantly change.
Conclusions: Our longitudinal study demonstrates that increased blinking may precede blepharospasm and that an abnormal blink reflex recovery cycle reflects the development of orbicularis oculi muscle spasms.

Blepharospasm (BSP) is a focal dystonia characterized by involuntary, bilateral, and usually symmetrical and prolonged spasms of the orbicularis oculi (OO) muscles.[1–4] Other relevant phenomenological features include increased blinking.[5] An enhanced blink reflex recovery cycle is a characteristic neurophysiological feature of BSP.[6–10]

It has been hypothesized that increased blinking is an early manifestation of BSP. A previous study by our group, in which individuals with increased blinking alone were compared with patients who had typical BSP, showed that the blink reflex recovery cycle was normal in the increased blinking group but was abnormal in the BSP group.[11] Somatosensory temporal discrimination threshold (STDT) abnormalities, a putative endophenotypical trait in dystonia,[12] were observed in both groups of patients. Our cross-sectional observation lends support to the hypothesis that patients with increased blinking may have a dystonic trait[11] despite not having clear dystonic manifestations. To date, no longitudinal studies have been performed to investigate whether patients with increased blinking alone develop BSP over time.

In the current study, patients with increased blinking as the sole manifestation in an earlier study[11] were clinically re-evaluated 5 years later to collect longitudinal information on the relationship between increased blinking and BSP. A neurophysiological assessment was also performed at follow-up to determine whether clinical changes were associated with physiological changes.

Patients and Methods

Eleven of the 16 patients with increased blinking as the sole manifestation who participated in the earlier study[11] were enrolled in the current 5-year follow-up study (Table 1). The remaining 5 patients could not be tested, because 1 died and the other 4 were lost to follow-up. Fifteen healthy individuals who were matched to the age of patients at follow-up (9 women and 6 men; ages 72 ± 1 years) were used as a control group for the recovery cycle of the R2 component of blink reflex and STDT. Written informed consent was obtained from all participants, and the experimental procedure was approved

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Keywords: blepharospasm, blink reflex recovery cycle, dystonia, increased blinking, movement disorders.
Relevant disclosures and conflicts of interest are listed at the end of this article.
The first two authors contributed equally to this study.
Received 2 February 2017; revised 7 March 2017; accepted 31 March 2017.
Published online 2 June 2017 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12499

doi:10.1002/mdc3.12499

by the Institutional Review Board At Sapienza University of Rome and was conducted in accordance with the Declaration of Helsinki.

The 5-year follow-up assessment of the 11 patients was performed according to the procedures used in the previous study[11] and at least 4 months after a botulinum toxin treatment. Participants were video recorded according to a standardized protocol.[13] BSP severity was assessed by means of the Blepharospasm Severity Rating Scale.[13] 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.[5,11,13] Two blinks were considered 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.[1,3,7] An experienced neurologist who was unaware of the study objectives reviewed the video recordings from this study and the previous study.

The blink reflex recovery cycle was studied according to the experimental procedure reported in previous studies.[6–11,14] The results of the blink reflex recovery cycle were reviewed by a neurophysiologist who was blinded to the results of the clinical assessment. We also calculated the R2 recovery index.[10,11] STDT was performed according to the experimental protocol reported in previous studies.[11,12,15,16]

Data were expressed as means ± standard errors and were analyzed using SPSS software. Two-way analysis of variance (ANOVA) with the factor FOLLOW-UP (enrollment and 5-year follow-up) and the factor interstimulus interval (ISI) (250, 500 and 1.000 msec) was used to compare the blink reflex recovery cycle at the follow-up and baseline assessments for each patient. Between-group, repeated-measures ANOVA with factor ISI as the main factor was used to analyze the blink reflex recovery cycle in patients and healthy controls. We then performed Mann-Whitney *U* tests to compare the R2 recovery index at the follow-up assessment between patients who did and did not develop OO spasms. Paired-sample *t* tests were used to analyze changes in STDT values at follow-up and baseline assessments for each patient. Unpaired-sample *t* tests were used to compare STDT values between patients at enrolment and healthy controls. Spearman rank correlation coefficients were computed to test possible correlations between variables. All P values < 0.05 were considered to indicate statistical significance.

Results

At the follow-up examination, the video recording showed that 9 of 11 patients had OO muscle spasms, whereas there was no evidence of OO spasms in the first video recording evaluation in any of the patients; the 2 patients without OO spasms (Table 1, Patients 1 and 6) continued to manifest increased blinking alone.

A repeated-measures ANOVA evaluating changes in the blink reflex recovery cycle in patients at the 5-year follow-up with the measurement obtained at the first assessment revealed significance of the factor FOLLOW-UP ($F_{[1,10]} = 49.4$; $P < 0.001$), the factor ISI ($F_{[2,20]} = 19.9$; $P < 0.0001$), and the interaction ISI × FOLLOW-UP ($F_{[2,20]} = 11.4$; $P = 0.001$). There was less inhibition of the conditioned R2 area at the 250-msec and 500-msec ISIs at the follow-up evaluation compared with inhibition at the baseline evaluation (250-msec ISI, $P < 0.0001$; 500-msec ISI, $P = 0.001$) (Fig. 1). Mann-Whitney *U* tests comparing R2 recovery index scores between the 9 patients who developed OO spasms and the 2 patients who had increased blinking as the sole manifestation revealed that the 2 subgroups significantly differed ($P = 0.03$). A between-group ANOVA comparing the blink reflex recovery cycle in patients

TABLE 1 Demographic, clinical, and neurophysiologic data from patients enrolled in the study

Patient*	Sex	Age, y	Disease duration, y	OO spasms at 5-year FU	Disease severity at 5-year FU†	R2 index, %		TDT, msec	
						Baseline	At 5-year FU	Baseline	At 5-year FU
1	Man	85	30	No	3	31	67	90	100
2	Woman	71	8	Yes	17	43	102	120	120
3	Woman	60	10	Yes	16	33	67	110	120
4	Man	60	5	Yes	12	38	84	160	160
5	Man	80	20	Yes	14	64	91	150	150
6	Man	67	15	No	3	43	63	130	140
7	Woman	75	13	Yes	6	25	72	140	133
8	Woman	77	5	Yes	6	28	76	130	120
9	Man	82	16	Yes	4	34	74	70	130
10	Woman	75	24	Yes	13	41	77	100	120
11	Woman	85	15	Yes	9	33	85	160	165
12	Woman	64	20	—	—	53	—	100	—
13	Woman	85	27	—	—	33	—	126	—
14	Man	72	10	—	—	37	—	128	—
15	Man	69	22	—	—	30	—	130	—
16	Man	63	18	—	—	26	—	128	—

R2, recovery index; TDT, temporal discrimination threshold; OO, orbicularis oculi; FU, follow-up.
*Age and disease duration of Patients 12 through 16 (lost at FU) are those at baseline.
†Disease severity was rated according to the Blepharospasm Severity Rating Scale (range, 1–18; Defazio et al., 2015[13]).

doi:10.1002/mdc3.12499

at follow-up with that in healthy controls revealed significance of the factor ISI ($F_{[2,48]} = 26.5$; $P < 0.0001$), the factor GROUP ($F_{[1,24]} = 110.4$; $P < 0.0001$), and the interaction ISI × GROUP ($F_{[2,48]} = 11.2$; $P < 0.0001$) (Fig. 1).

At the follow-up assessment, Spearman coefficient (r) values yielded a significant positive correlation between the R2 recovery index and the BSP total severity score (r = 0.68; $P = 0.01$). No significant relationship was observed between the R2 recovery index and age (r = 0.06; P = 0.85). STDT values were higher than normal at the enrollment assessment ($P = 0.00007$) and remained unchanged at the follow-up assessment ($P = 0.22$) (Table 1).

Discussion

This study provides longitudinal clinical and neurophysiological data from 11 patients who initially presented with increased blinking as their sole symptom, a normal blink reflex recovery cycle, and an abnormal STDT.[11] At the 5-year follow-up examination, OO spasms had developed in 9 of 11 patients, and the R2 recovery cycle had become abnormal. We also observed a significant correlation between BSP severity and the R2 recovery index at follow-up. This longitudinal observation indicates that increased blinking may precede the appearance of BSP. The abnormal STDT values were unchanged at the follow-up assessment.

In our previous report, we suggested that patients with increased blinking had a dystonic trait[11] despite having a normal blink reflex recovery cycle, because their STDT was abnormal. An altered STDT is considered an endophenotypical feature of dystonia, because it is present in both affected and unaffected body parts in patients with different types of focal dystonia as well as in patients' unaffected relatives.[12,15] We now demonstrate that, at the follow-up assessment, 9 of the 11 patients had developed OO spasms and abnormal R2 inhibition. This study demonstrates that increased blinking alone can be considered a prodrome of dystonia. Therefore, increased blinking accompanied by increased STDT values may be highly suggestive of dystonia. The current study also demonstrates that abnormal R2 inhibition parallels the development of OO spasms. The enhanced blink reflex recovery cycle is a neurophysiological feature in BSP.[6–11] The correlation we observed between the BSP severity score and the R2 recovery index at the follow-up assessment suggests that disease severity may increase as a consequence of reduced brainstem inhibition, with the R2 recovery index as a biomarker.[11] Consistent with this, the R2 recovery index differed between the 9 patients who had developed OO spasms (and also had higher disease severity scores) and the 2 patients who did not develop OO spasms (who also had low disease severity scores at follow-up). Because the 2 patients with increased blinking who did not develop BSP had modest changes in their blink reflex recovery cycle at the 5-year follow-up assessment compared with the enrolment assessment, we may hypothesize that they will likely develop prolonged spasms and an abnormal R2 recovery cycle in the future.

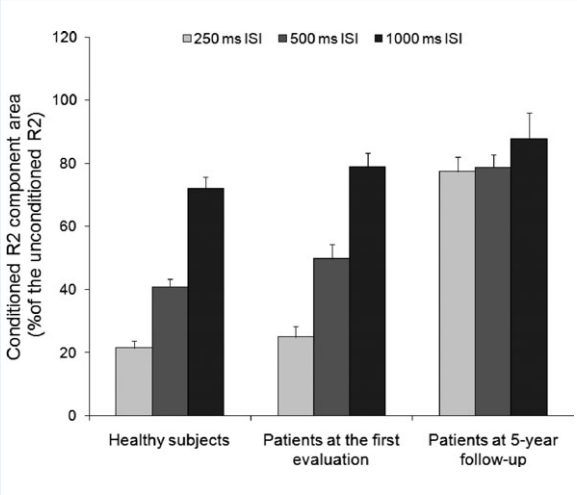

Figure 1 The blink reflex recovery cycle is illustrated in the 11 patients who had increased blinking alone at the first evaluation, in the same patients tested at 5-year follow-up, and in healthy individuals. Each column represents mean values, and bars represent standard errors. ISI, interstimulus interval.

It is worth noting the differences in significance of the 2 physiological tests used here. The STDT is an endophenotypical biomarker, as are most of the physiological measures that have been identified. It is abnormal before the spasms are manifest and does not correlate with the development of the disorder or disease severity. The R2 recovery index is a biomarker of the BSP itself and does not develop until the spasms appear; then, it correlates with the severity of the disorder. This cannot be said for any other physiological measure in any type of dystonia. The R2 recovery index is only abnormal when there is dystonia in the cranial territory, again indicating its direct relevance to disease. Both the STDT and the R2 recovery index assess inhibitory mechanisms; and it would be valuable to identify why they have different correlations.

A limitation of the study is that the follow-up assessment was performed only in 11 of the 16 patients enrolled in the earlier study. However, it should be borne in mind that patients with increased blinking alone are relatively rare. The longitudinal study design and the long-lasting follow-up, on the other hand, are features that strengthen the current findings. Patients underwent the same video-recording protocol in the 2 assessments, which is likely to have ruled out any bias in the recognition of the clinical features. Finally, the clinical assessments were performed by 1 examiner who was unaware of the study objectives, just as the blink reflex recovery cycle measurements were performed by 1 examiner who was blind to the clinical assessment. A limitation of the neurophysiological study may be that the follow-up assessment did not include the same group of healthy controls enrolled in the earlier study. However, the aim of the neurophysiological study was to evaluate the physiological changes accompanying the appearance of BSP.

doi:10.1002/mdc3.12499

In conclusion, our longitudinal study demonstrates that, at least in a proportion of patients, increased blinking may precede BSP, and an abnormal blink reflex recovery cycle is associated with the development of OO spasms.

Author Roles: 1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript preparation: A. Writing the First Draft, B. Review and Critique.

A.C.: 1A, 1B, 2B, 3A
G.F.: 1A, 2A
G.D.: 3B
M.H.: 3B
G.F.: 2A, 2B
A.B.: 1A, 3A

Disclosures

Ethical Compliance Statement: 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.

Funding Sources and Conflict of Interest: The authors report no conflict of interests.

Financial Disclosures for the previous 12 months: A. Conte received funds from Sapienza University of Rome for a research project on movement disorders. G. Ferrazzano reports no funding and no conflicts of interest. G. Defazio received funds from the Benign Essential Blepharospasm Research Foundation for research on blepharospasm; funds from the Italian Ministry of University for a research project on dystonia; and honoraria for symposia from Boehringer Ingelheim, Lundbeck, GlaxoSmithKline, and UCB. G. Fabbrini has received funds from Sapienza University of Rome for research projects on movement disorders. M. Hallett serves as chair of the Medical Advisory Board for and may receive honoraria and funding for travel from the Neurotoxin Institute; he is involved in the development of Neuroglyphics for tremor assessment and has a collaboration with Portland State University to develop sensors to measure tremor; 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 National Institutes of Health (NIH) (from Brainsway) for licensing of this patent; he is on the editorial board of 20 journals and receives royalties and/or honoraria for publishing from Cambridge University Press, Oxford University Press, John Wiley & Sons, Wolters Kluwer, Springer, and Elsevier; Dr. Hallett's research at the NIH is largely supported by the NIH Intramural Program; supplemental research funds have been granted by UniQure for a clinical trial of AAV2-GDNF for Parkinson's disease, by Merz for treatment studies of focal hand dystonia, and by Allergan for studies of methods to inject botulinum toxins. A. Berardelli received funds from the Benign Essential Blepharospasm Research Foundation for research on blepharospasm; national grants from the Italian Ministry of University and Sapienza University of Rome, Chiesi, Lundbeck, Merz, Allergan, Ipsen; and honoraria for lecturing from Boehringer Ingelheim, GSK Pharmaceutical, Novartis Pharmaceuticals, Lundbeck, and Chiesi.

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doi:10.1002/mdc3.12499