a basis for future studies on the epidemiology of PD, combining clinical surveys and the unique registries of Denmark.

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Analysis of Blink Rate in Patients with Blepharospasm

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Abstract: **The blink rate (BR) during rest, conversation, and reading was assessed in 50 patients with blepharospasm (BS) and in 150 healthy subjects. BR at rest and during conversation was higher in patients with BS. Moreover, 76% of patients had BR higher at rest than during conversation, whereas in 74% of controls, BR was higher during conversation than at rest. The sensitivity and specificity of two parameters (value of BR at rest and pattern *rest-BR higher than conversation-BR*) in discriminating patients and controls were computed. The best fit was obtained with a rest-BR above 27 blinks per minute. When the two parameters were combined (rest-BR above 27 blinks**

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per minute together with the pattern *rest-BR higher than conversation-BR*), we obtained a 92.3% sensitivity and a 82.0% specificity in discriminating between BS patients and controls. These findings indicate that specific features of BR can be associated with BS, suggesting that the analysis of BR might be helpful for the diagnosis of BS in early stages.

Key words: blepharospasm; blinking; dystonia

Blepharospasm (BS) is the focal dystonia involving orbicularis oculi muscle (and periocular muscles), resulting in involuntary and forceful eyelid closure. Approximately 78% of patients with BS[1] report that the presenting symptom was increased blink rate (BR), corresponding to stage I of BS in the Burke & Fahn dystonia rating scale (BFDRS).[2] After a variable time interval, a sustained nonforceful closure of eyelids occurs (stage II) and when dystonia worsen, forceful spasms become evident (stage III). In the most severe cases, the spasmodic closure takes over and patients suffer a "functional blindness" (stage IV). According to the currently accepted clinical definition of dystonia,[3,4] a similar progression of the abnormal involuntary movement is common to other forms of dystonia. A definite diagnosis of BS is possible only in the presence of spasms, as increased BR is not sufficient for the diagnosis and no diagnostic test is available.

Few studies are available on BR in large series of dystonic patients. A normal BR was reported in 9 dystonic patients.[5] More recently, abnormally high BR was observed in 48 patients with cervical dystonia and 14 with generalized dystonia with cranial–cervical involvement, whereas in patients with limb dystonia, BR was comparable to controls.[6] In such studies, the influence of different behavioral conditions on BR was not analyzed. The aim of this study was to analyze BR in patients with clinically definite BS, compared with 150 healthy subjects previously investigated.[7]

PATIENTS AND METHODS

A total of 50 consecutive patients (37 women and 13 men) with a clinical diagnosis of BS in stages 2 to 4 of the BFDRS[2] were included in the study. A total of 42 patients were affected by BS, 4 by Meige's syndrome, 3 by cranial–cervical dystonia, and 1 by multisegmental dystonia. The mean age of patients was 65.3 ± 9.3 years (range, 46–83 years); the mean disease duration was 7.2 ± 4.8 years (range, 1–31 years). Exclusion criteria were secondary dystonia, psychiatric conditions, use of psychoactive drugs, ocular allergies, conjunctivitis, or any other condition of ocular distress in the last 3 months. Because botulinum toxin (BoNT) may influence the blink reflex by weakening orbicularis oculi muscles,[8] patients treated with BoNT were examined at least 3 months after the last treatment, when they were fully symptomatic and the strength of orbicularis oculi recovered.

A blink was defined as any visible, bilateral, and synchronous contraction of orbicularis oculi muscle,[6] causing an eyelid drop. Sustained spasms of orbicularis oculi muscle were not considered blinks. BR was expressed as blinks per minute. BR was computed during three behavioral conditions: conversation, reading, rest. BR at rest was assumed as the basal condition and compared with conversation and reading. To obtain reproducible experimental conditions, patients and controls underwent exactly the same study protocol, which was described in a previous study[7] and is here summarized. Accordingly, the condition sequence (conversation, reading, rest), topics of conversation, and the passage proposed for reading were exactly those previously reported.[7]

Three videotape segments were recorded, in the following order: (1) free conversation on trivial subjects, bearing no emotional impact and requiring no memory recall; (2) reading a difficult book paragraph, requiring mental concentration; (3) quiet rest with opened eyes. Each segment was recorded for 150 seconds. The first 20 seconds of recording were not analyzed, to allow subjects to adapt to the environment. Two independent observers reviewed the videotapes and measured the number of blinks for 2 minutes of each segment. The two measures were averaged. The same examiners videotaped and computed BR in both controls and patients. All patients signed an informed consent after the videotape recording was completed, because it was mandatory that patients were unaware of the purpose of the study.

The BR of patients was compared with BR of 150 healthy volunteers.[7] Because BR values were not normally distributed, comparisons between groups were carried out by means of nonparametric Mann–Whitney U test and the data were expressed as median values, 5th, 10th; 90th, 95th percentiles. To estimate sensitivity and specificity of BR values in discriminating between patients and controls, a receiver operating characteristic (ROC) curve was plotted. The point closest to 80% sensitivity and 80% specificity was defined as the best trade-off threshold discriminating the two groups.

RESULTS

The median values of BR in patients and controls during rest, reading, and conversation are reported in Table 1. In patients with BS, the median rest-BR was 55, median conversation-BR was 31.5, whereas median

TABLE 1. *Median blink rate (range | 5^{th}, 10^{th}; 90^{th}, 95^{th} percentiles) in control and blepharospasms groups*

	Control group			Blepharospasm group		
	Total	Men	Women	Total	Men	Women
Rest	17[a] (2.5–59 | 4, 6; 40, 48)	15.6	18	55[a] (17–131 | 20, 24; 95, 102)	50.1	58.3
Conversation	26[b] (6.25–68 | 11, 13; 47, 53)	24	26.7	31.5[b] (10–123 | 20, 17; 82, 93)	33.9	43.8
Reading	4.5 (0.5–40.5 | 0.7, 1; 16, 22)	3.0	6.2	4 (0.5–38 | 0.5, 0.5; 28, 32)	5.1	8.5

[a]Significantly different, $P < 0.0001$.
[b]Significantly different, $P = 0.0057$.

reading-BR was 4. When BR values in patients were analyzed according to sex, median BR was higher among women across all behavioral conditions, even if such difference was not statistically significant. As compared with rest, BR decreased by 44% during conversation ($P = 0.0018$) and by 91% during reading ($P < 0.0001$). In 38 patients (76%), rest-BR was higher than conversation-BR, whereas in 12 patients (24%), BR was lower at rest than during conversation. In all patients, BR during reading was considerably lower than BR during conversation or at rest.

As compared with controls, BR was significantly higher in BS patients both at rest ($P < 0.0001$) and during conversation ($P = 0.0057$). No significant difference in BR was observed between the two groups during reading (Fig. 1A). Among controls, the pattern *conversation-BR > rest-BR > reading-BR* was the most common (63% of the subjects). By contrast, the pattern *rest-BR > conversation-BR > reading-BR* was observed only in 22.7% of controls. Other less-common patterns were detected in lower percentages of controls.[7] For each pattern, Fisher's exact probability test or χ^2 test with Yates correction were used, to compare frequency distribution between patients and controls. As even the raw values of reading-BR overlapped in healthy and dystonic subjects, this condition was not analyzed further.

The pattern *rest-BR > conversation-BR* was more frequent among patients (76.0%) than among controls (24.7%), with a highly significant difference in frequency distribution between the two groups ($P <$ 0.0001). By contrast, the pattern *conversation-BR > rest-BR* was more frequent among controls (74.0%) than among patients (24.0%), with a highly significant difference in frequency distribution between the two groups ($P < 0.0001$). The pattern *conversation-BR = rest-BR* was observed only in 2 of 150 normal subjects (1.3%) and in no patient, without significant differences in frequency distribution between the two groups. In summary, only two patterns were detected in BS group, namely *rest-BR > conversation-BR > reading-BR* as observed in 76% of patients and *conversation-BR > rest-BR > reading-BR*, as observed in 24% of patients.

Sensitivity and specificity of two parameters (rest-BR and the pattern *rest-BR > conversation-BR*) in discriminating between patients and controls was estimated. When considering rest-BR, the best discriminating value was 27 blinks per minute (Fig. 1B). By assuming BR at rest >27 as a feature associated to BS, we found a sensitivity of 90.0% (confidence interval [CI], 78.6%–95.7%), a specificity of 70.9% (CI, 63.2%–77.7%), a positive predictive value (PPV) of 51.1% (CI, 40.9%–61.3%) and a negative predictive value (NPV) of 95.5% (CI, 89.9%–98.0%). The association of BS with *rest-BR > conversation-BR* showed a sensitivity of 76.0% (CI, 62.6%–85.7%), a specificity of 79.7% (CI, 72.5%–85.4%), a PPV of 55.9 (CI, 44.1%–67.1%), and a NPV of 90.8 (CI, 84.6%–94.6%). When these two parameters were combined, sensitivity was 92.3% (CI, 79.7%–97.3%), specificity was 82.0% (CI, 73.8%–88.0%), PPV was 64.3 (CI, 51.2%–75.5%), and NPV was 96.8% (CI, 91.0%–

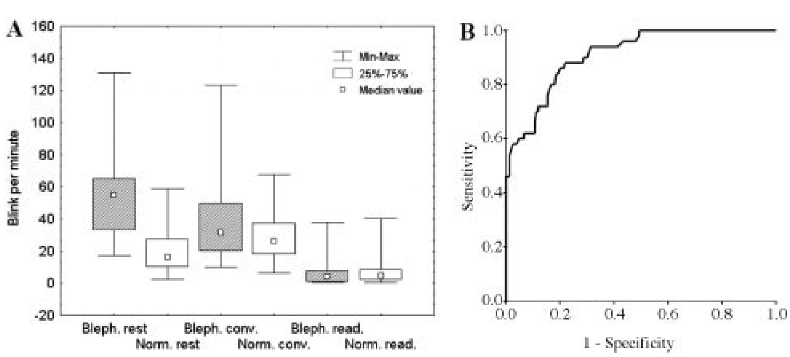

FIG. 1. A: Median values (25th and 75th percentiles, range min-max) of blink rate (BR) at rest in patients (Bleph.) and in controls (Norm.) in different behavioral conditions (rest., at rest; conv., during conversation; read., during reading). **B:** Receiver operating characteristic (ROC) curve displaying sensitivity and specificity for the value of BR discriminating the group of controls from the group of patients. The best discriminating value was 27 blinks per minute with sensitivity and specificity of 90.0% and 70.9%, respectively.

98.9%). When considering the subgroup of 12 BS patients (24% of the sample) who did not present the feature *rest-BR > conversation-BR*, we observed that only 3 of them failed to meet also the criterion of BR at rest >27.

DISCUSSION

The patients with clinically definite BS described in this study had demographic characteristics similar to those of patient reported in other published series.[9] Because the clinical hallmark of dystonia is sustained spasmodic muscle contraction, we did not include patients in stage I to minimize bias in diagnosis.

The analysis of BR in different behavioral conditions showed that, in most patients with BS, *rest-BR* was higher than *conversation-BR*, whereas the pattern *conversation-BR > rest-BR* was observed in the large majority of controls.[7] These findings support the view that conversation may act as a *gest antagonistique* toward a pathologically increased BR. According to Fahn, approximately 60% of patients achieve a reduction of spasms during conversation, while the opposite occur for most forms of dystonia, which get worse during action.[4] In healthy subjects, conversation increases BR, probably because speech is a mental activity (which is known to enhance BR[10]) and because the mimic is used to underlie and confer punctuation to speech.[11] Although attention is likely to modulate BR in both BS patients and controls, the mechanisms of such attentional control are still poorly known.

Because the inhibition of BR induced by conversation might be a specific feature of dystonic patients, we hypothesize that the analysis of BR features could be helpful in the diagnosis of BS in patients without muscle spasms, who have an increased rest-BR.

The association of rest-BR >27 with BS showed a 90.0% sensitivity, but low specificity (70.9%). Actually, rest-BR largely overlapped between the two groups, because more than 40% of patients had a rest-BR lower than 48, corresponding to 95th percentile in our controls and close to the value discriminating between controls and patients with BS in a previous series.[6] Conversely, the pattern *rest-BR > conversation-BR* is more specific (79.7%) in discriminating controls and patients, but less sensitive (76.0%). When the two parameters (rest-BR > 27 and *rest-BR > conversation-BR* pattern) were combined, a reasonably high sensitivity (92.3%) and specificity (82.0%) in discriminating between patients and controls was obtained. Accordingly, we propose that the combination of a BR at rest >27 together with the pattern *rest-BR > conversation-BR* is a feature frequently associated with BS.

In patients with BS, the occurrence of eyelids spasms could decrease BR by both decreasing the available time for spontaneous blinking and reducing the stimuli for spontaneous blinking, as eyelid spasms may fulfill the function of normal blinking.[12] Accordingly, it might be hypothesized that BS patients in stage I might have higher BR values compared with patients in more advanced stages. If so, even more clear-cut differences in BR values and patterns should be observed between controls and patients in stage I, compared with what observed in the comparison between controls and patients in stages II to IV. It might be speculated that, in BS patients, an increased rate of blinking and an altered task-induced BR pattern (*rest-BR > conversation-BR*) may precede spasms. However, because the correlation between severity of dystonia and BR is still poorly known, the features of blinking in early stages of BS should be prospectively investigated.

Indeed, an increased BR is not specific of BS,[1,12] as it can be observed in other conditions (Huntington's disease,[5] tardive dyskinesias,[13] Gilles de la Tourette's syndrome,[14] schizophrenia[15]), including ocular discomfort due to ophthalmologic disorders. However, the only condition difficult to diagnose in patients with overactivity of periocular muscles, is chronic tic, because all the other above-mentioned conditions show clinical features that may support the diagnosis. In conclusion, our findings suggest that the analysis of BR, which can be carried out easily during clinical examination without instrumental tools,[6] together with available clinical scales, might improve diagnostic accuracy in patients in initial stages of BS.

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Protein Intake in Parkinsonian Patients Using the EPIC Food Frequency Questionnaire

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Abstract: **The dietary habits of 45 Italian patients with Parkinson's disease (PD) and their spouses were investigated using the EPIC food frequency questionnaire. Average daily energy intake was similar, but PD patients consumed significantly more vegetable proteins and carbohydrates (both +18%; $P = 0.01$ and $P = 0.001$, respectively). Daily protein intake, which interferes with levodopa absorption, was 50% higher than the recommended daily allowance (1.2 vs. 0.8 g/kg) in both PD patients and spouses and was significantly higher in patients with moderate/severe symptoms (1.27 ± 0.29 vs. 1.07 ± 0.28 g/kg; $P < 0.001$). In patients taking levodopa, there was a correlation between daily levodopa dosage and protein intake ($P = 0.027$). Dietary habits of patients with advanced and/or fluctuating PD should always be checked, with particular reference to protein intake.** © 2006 Movement Disorder Society

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Key words: Parkinson's disease; diet; protein intake; levodopa

An accurate evaluation of dietary habits in Parkinson's disease (PD) is important to assess the clinical response to pharmacological therapy. It is well known that the amount and daily distribution of protein intake affect clinical response to levodopa by increasing plasma levels of large neutral amino acids (LNAAs), which compete with levodopa carriers both in the blood–brain barrier and in the intestinal mucosa.[1–5]

Guidelines for the management of PD recommend the restriction of daily protein intake to the recommended daily allowance (RDA) and protein redistribution mainly to the evening meal in fluctuating patients.[6,7] We investigated the dietary habits of PD patients attending for the first time the Nutrition Unit compared with those of their spouses, with particular reference to protein intake.

PATIENTS AND METHODS

The subjects were outpatients living and eating at home who were recruited consecutively among the patients affected by PD diagnosed according to the U.K. Brain Bank criteria,[8] attending for the first time the Nutrition Unit of Parkinson Institute, Milan. The control group was composed of their healthy spouses. PD patients were not following any diet because of concomitant diseases, and the same was true for controls.

All of the subjects gave their written informed consent for this study.

Patients were examined after an overnight fast by a physician specialized in nutrition, who registered body weight and height, current therapy, and PD duration and staging.

A neurologist with experience in movement disorders determined the Hoehn and Yahr score (1–2 = mild; ≥ 2.5 = moderate/severe) and scores on the Unified Parkinson's Disease Rating Scale (UPDRS), noting the total score, the motor score, and the score related to activities of daily living (ADL), in both the *on* and the *off* phase. Mini Mental State Examination score was determined (MMSE < 23 were excluded). Controls were interviewed to check that they were not following any particular diet on account of concomitant diseases; their body weight and height were measured.

Subjects were then assisted by a trained nutritionist in completing the European Prospective Investigation into Cancer and Nutrition (EPIC) questionnaire, a structured semiquantitative food frequency questionnaire of 302 different food items, about dietary habits in the previous year. The questionnaire had been previously validated for the Italian population.[9]