Buccopalpebral reflex in Parkinson disease and blink reflex study

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ABSTRACT

الأهداف: التعريف بمنعكس بدائي يدعى بمنعكس الشدق الجفني والتحقق من هذا الشدق طبياً وعصبياً في المرضى المصابين بمرض باركسون.

الطريقة: أجريت دراسة مستقبلية شملت 17 مريض (9 مريض مصاب بمنعكس الشدق الجفني و 7 مريض غير مصاب بمنعكس الشدق الجفني) وذلك في مستشفى مركز أبحاث أنقرة للتدريب، أنقرة، تركيا خلال الفترة من يناير إلى ديسمبر 2008م. تم تشخيص المرضى جميعاً بالمرض بدون أي عقارات طبية وصفت لهم. باستخدام طريقة منعكس الطرف تم تحريض 3 فروع من العصب الثلاثي التوأمي. إضافة إلى ذلك كان اختبار الحالة العقلية المصغر، ومؤشر مقياس مرض باركسون ومقياس ياهر وهويهن وتكرار المنعكس، وفترة الإصابة بمرض باركسون متوافق بين المجموعتين.

النتائج: في المرضى المصابين بمنعكس الشدق الجفني، 5 مرضى لديهم رعاش، و 4 الباقين لديهم بطء بالحركة كعرض مسيطر بينما المرضى الآخرين غير المصابين كان لديهم رعاش. وعندما قمنا بمقارنة منعكس الطرف بين المجموعتين تم الحصول على R2 بمؤثر فوق الحجاج والذي كان أقل لدى المرضى المصابين بإصابة إيجابية بمنعكس الشدق الجفني. لم يكن هنالك أي اختلاف إحصائي مهم من ناحية اختبار الحالة العقلية المصغر، ومؤشر مقياس مرض باركسون، ومقياس ياهر وهويهن، وتكرار المنعكس ، وفترة الإصابة بمرض باركسون بين المجموعتين.

خاتمة: أشارت هذه الدراسة أن المنعكس يعتبر مؤشر للحساسية ويقلل من مستوى العتبة مثل أعراض ميرسون حيث لا يوجد كبح لمنعكس المقطب. كما أن نتائج منعكس القرنية تدعم هذه الفرضية.

Objectives: To define a new primitive reflex named the buccopalpebral reflex (BPR), and to investigate this reflex clinically and neurophysiologically in patients with Parkinson disease.

Methods: This prospectively designed study included 17 patients, 9 BPR positive patients, and 8 BPR negative patients in Ankara Research and Training Hospital, Ankara, Turkey, and was carried out between January and December 2008. All patients had Parkinson disease without any medication. Using the blink reflex technique, 3 branches of the trigeminal nerve were stimulated. Additionally, the Mini Mental State Examination (MMSE), the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr Score (HYS), the blink frequency, and the duration of Parkinson disease was also matched between the 2 groups.

Results: In patients with positive BPR, 5 had tremor and the remaining 4 had bradykinesia as a dominant symptom, while all other patients with negative BPR had only tremor. When blink reflex findings were compared between the 2 groups, R2 and contralateral R2 latencies that were taken by supraorbital stimulus were significantly shorter in the BPR positive patients. There were no statistically significant differences in terms of MMSE, UPDRS, HYS, and frequency of blinking, and duration of illness between the 2 groups.

Conclusion: This reflex may be an indicator of sensitivity or decrease of threshold level such as Myerson's sign, in which there is no inhibition in glabella reflex. The blink reflex findings support this hypothesis.

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Pathological reflexes, which are generally observed during widespread brain diseases in adults, are referred to as primitive reflexes. Primitive reflexes may also be added to the clinical picture of Parkinson's disease, as is the case with other neurodegenerative diseases. The most common of these is an increase in the glabellar reflex, snout reflex, palmomental reflex (PMR), and the sucking reflex.[1] Blinking is a complex of movements consisting of voluntary and spontaneous reflexes aimed at protecting the eye, and which is elicited by a variety of stimuli.[2] Due to an antagonistic interaction between the orbicularis oculi muscle and the levator palpebrae superior muscle, the eyelid closes rapidly followed by a slow opening movement. These voluntary, spontaneous, and reflex movements are all involved in blinking of the eye.[3] The rate of eye blinking is controlled by the dopaminergic pathway of the striatonigral circuit.[4,5] Various studies have demonstrated that the frequency of eye blinking is less in patients with Parkinson's disease than in controls.[6]

In our clinical observation, eye blinking together with shrinking of lips was observed by the percussion of the upper lip in neurodegenerative diseases such as Parkinson's disease. We believe that this reflex is a more complex primitive reflex than the glabella and snout because of the shrinking of lips simultaneously with blinking. We have termed this reflex the buccopalpebral reflex (BPR). In this study, we investigated BPR in idiopathic Parkinson disease both clinically and electrophysiologically.

Methods. Patients with idiopathic Parkinson disease who were not undergoing any treatment for Parkinson disease were included in this prospective study. The patients were divided into 2 groups (BPR positive patients and BPR negative patients). All were admitted and/or followed up in the outpatient clinic of the SB Ankara Training and Research Hospital, Ankara, Turkey between January and December 2008. The study was designed according to the principles of the Helsinki Declaration and approved by the local ethical committee.

The diagnosis of Parkinson's disease was made by 2 separate neurologists according to published criteria.[7] Each of the Parkinson's disease patients completed standard forms with demographic information (such as age and gender), disease related information (disease duration, baseline dominance, Unified Parkinson's Disease Rating Scale [UPDRS] scores), and personal medical history. Secondary causes of parkinsonism, such as drugs, intracranial hemorrhage, calcification, trauma, infarction, multi system atrophy (MSA), and progressive supranuclear palsy (PSP), were excluded by clinical examination, imaging techniques, and personal medical history. Patients with Parkinson-plus syndrome, secondary Parkinsonism or patients receiving dopaminergic therapy were not included in this study. Patients who had diabetes mellitus and thyroid disease, high fasting blood glucose levels, hypothyroidism, vitamin B12 and folic acid deficiency, abnormality on cranial MRI, or peripheral neuropathy on nerve conduction study were excluded from the study. Nine patients (3 male, 6 female) with positive BPR, and 8 (2 male, 6 female) patients with negative BPR were included in the study. Ten age-gender matched normal individuals formed the control group.

The age, gender, disease duration, dominant symptom, UPDRS score (total, mentation, behavioral, and mood, daily life activities, and motor system), Hoehn-Yahr score, and Mini Mental state score (total, recording, and memory retrieval) of all the patients were evaluated. The blink reflex of all the patients was elicited through supraorbital, infraorbital, and mental stimulation. The average number of blinking movements per minute was also assessed by EEG with the eyes open, and the data were compared between the BPR positive group and BPR negative group.

The blink reflex study was performed using the Medelec Synergy device (VIASYS Healthcare Inc., Old Woking, Surrey, UK). The filter limits were 10 Hz-10 kHz while the sweep rate was 100 msec. The duration of each electrical stimulus was 0.05 msec, with an interstimulus interval of 5 msec. Patients lay supine on the operating table and were examined with their eyes slightly closed. Surface electrodes were used during the investigation. The surrounding area of the patient's eye was cleaned with alcohol. The active electrode was placed laterally on the lower lid while the reference electrode was placed on the wing of the nose. The blink reflex study was performed by stimulating each of the 3 trigeminal nerves consecutively; by order of supraorbital, infraorbital, and mental branches (**Figure 1**). The degree of stimulation was slowly increased to the pain threshold, and the measurement was carried out when the degree of stimulus was just below the painful threshold. As a result, it seems that they used the same intensity for all participants. Every point was stimulated at least 8 times at intervals of 30 seconds. The first negative potential, which occurred following the stimulus artifact during ipsilateral stimulation, was referred to as R1, and the second as R2; the negative potential, which occurred almost at the same time as R2, at the second channel, was referred to as contralateral

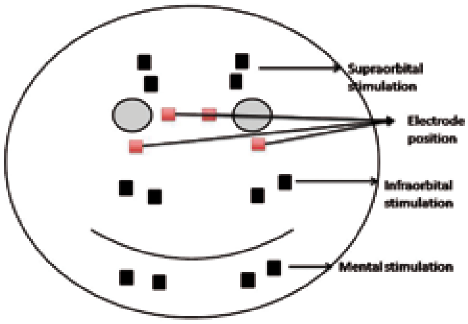

Figure 1 - The active electrode is placed laterally on the lower lid while the reference electrode is placed on the wing of the nose (red boxes). The blink reflex study was performed by stimulating each of the 3 trigeminal nerves, supraorbital, infraorbital and mental stimulations (black boxes).

R2. Latency was measured from the starting points of these negative potentials. Latency of the earliest and latest responses for R1, R2, and contralateral R2 were measured, and the difference between the latest and earliest responses of R1, R2, and contralateral R2 were also calculated. All these results (earliest response for R1, R2, and contralateral R2, and differences between the latest and earliest responses for R1, R2, and contralateral R2) were compared between age and gender matched normal individuals, buccopalpebral reflex positive and negative groups.

Data obtained were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0 for Windows program. The independent variable T test was used for group comparison. P-values of <0.05 were considered statistically significant.

Results. A total of 17 patients with idiopathic Parkinson's disease, 9 (52.9%) patients with positive BPR, and 8 (47.1%) patients with negative BPR were included in the study. Patients were divided into 2 groups; those with positive BPR and those with negative BPR, and all data were compared between the groups (**Table 1**). The results of the blink reflex study were also compared with age, and gender matched normal individuals (mean age: 66.40±4.35, 5 males, 5 females). Although disease duration was longer in patients with positive reflexes, no statistically significant difference was found between the 2 groups with regards to mean disease duration and mean age. In the BPR positive group, tremor was observed as a dominant symptom in 5 of the patients, while there was bradykinesia in 4 of the patients. However, tremor was the dominant symptom in all patients (8 patients) in the negative reflex group. No statistically significant difference was observed between total UPDRS, mentation-behavior-mood, daily life activity, and motor findings. Comparison of patients in both groups for the number of blinking movements per minute did not show significant differences (**Table 1**). Results of the blink reflex study are summarized in **Table 2.**

Supraorbital stimulation. A unilateral R1 response was not obtained in one patient with positive BPR using supraorbital stimulation. However, the R2 and contralateral R2 responses were bilaterally obtained in all patients with or without BPR. No significant difference was observed between the 2 groups with regards to R1 responses (p=0.52). However, latencies of the R2 (p=0.001) and contralateral R2 (p=0.024) responses were statistically significantly shorter in patients with positive BPR when compared to those with negative BPR. No significant findings were demonstrated in differences between the earliest and latest R1 (p=0.31), R2 (p=0.62), and contralateral R2 (p=0.60) responses. When we compared these results with normal individuals, there were no differences between normal individuals and patients with negative BPR in terms of R1, R2, and contralateral R2 in supraorbital stimulation. However, in supraorbital stimulations, latencies of the R2 and contralateral R2 responses were statistically significantly shorter in patients with positive BPR when compared to normal individuals

Infraorbital stimulation. In the reflex positive group, R1 responses were not obtained in 2 patients by maxillary stimulation unilaterally, and in 3 patients bilaterally, whereas R2 and contralateral R2 responses were obtained in all patients. The R1 responses were not obtained in 5 patients while the R2 and contralateral R2

Table 1 - Comparison of buccopalpebral reflex positive and negative patients.

Variable	Reflex (+)	Reflex (-)
Number of patients	9	8
Age (year)	60.77±14.69	64.00±8.66
Gender M/F	3/6	2/6
Disease duration (years)	4.30±2.00	3.37±2.04
Dominant symptom (tremor/ bradykinesia)	5/4	8/0
UPDRS (total)	34.0±11.44	27.5±10.73
MMSE	26.55±4.79	27.37±2.72
Blinking frequencies/min	18.0±8.29	20.0±14.6
Hoehn-Yahr	2.22±0.66	2.0±0.00

MMSE - Mini mental state examination, UPDRS - Unified Parkinson's disease Rating Scale, Reflex (+) - reflex positive, Reflex (-) - Reflex negative

Table 2 - Blink reflex study results in buccopalpebral reflex positive and negative patients.

Latency (msec)	Reflex (+)	Reflex (-)	Normal	*P*-value*
Supraorbital R1	11.10±0.81	11.30±1.0	11,46±0,88	0.52
Supraorbital R2	30.17±4.17	37.09±6.54	37.39±5.76	0.001
Supraorbital CR2	34.05±6.22	39.27±6.59	39.52±5.80	0.024
Supraorbital earliest and latest R1 difference	0.65±0.83	0.42±0.36	0.42±0.32	0.31
Supraorbital earliest and latest R2 difference	3.34±1.99	3.70±2.22	3.70±1.97	0.62
Supraorbital earliest and latest CR2 difference	3.41±2.44	2.95±2.71	2.96±2.41	0.60
Maxillary R1	12.35±1.39	13.55±0.73	13.25±0.80	0.07
Maxillary R2	37.51±5.41	38.08±3.66	38.41±2.99	0.75
Maxillary CR2	39.11±5.78	39.81±4.69	39.84±3.89	0.73
Maxillary R1 earliest and latest difference	0.66±0.28	0.90±0.61	0.90±0.52	0.31
Maxillary R2 earliest and latest difference	3.13±1.75	4.54±2.40	4.49±2.06	0.07
Maxillary CR2 earliest and latest difference	2.66±1.77	4.04±3.17	4.03±2.71	0.13
Mandibular R1	14.35	-	-	-
Mandibular R2	41.94±8.32	36.85±4.24	36.96±2.49	0.41
Mandibular CR2	42.43±8.26	37.52±5.26	37.67±3.10	0.43
Mandibular R1 earliest and latest difference	2.3	-	-	
Mandibular R2 earliest and latest difference	3.56±1.56	4.55±1.62	4.51±0.94	0.41
Mandibular CR2 earliest and latest difference	3.22±1.46	3.45±0.49	3.45±0.31	0.83

Reflex (+) - reflex positive; Reflex (-) - reflex negative, *Comparison of patients with positive buccopalpebral reflex to patients with negative buccopalpebral reflex and normal subjects

responses were not obtained in 2 patients bilaterally in the reflex negative group. No significant difference was demonstrated between the groups including normal individuals with regards to of R1, R2, and contralateral R2 responses, and the differences of the earliest and latest responses between 2 groups.

Mental stimulation. An R1 response was obtained unilaterally in one patient with positive BPR by mandibular stimulation. However, R2 and contralateral R2 responses were not obtained in one patient bilaterally, but were obtained in the other patients. No R1 response was obtained in the group with negative BPR, while R2 and contralateral R2 responses were obtained in only one patient bilaterally. There were no R1, R2, or contralateral R2 responses in normal individuals. The absence of response in these patients was not due to habituation.

Discussion. Various primitive reflexes are observed in patients with positive Parkinson's disease. The diagnostic importance of these reflexes, their relationship with the disease severity, and the underlying pathology are unknown.[8]

We did not find any definition in the literature of BPR as defined in this study. Palpebral reflexes may be summarized as follows: The eyes may close following reflex contraction of the orbicularis oculi muscle as a response to other stimuli. Reflex closure of the eyes in response to a sudden high voice is known as the auditory palpebral, auropalpebral, acousticopalpebral, or cochleopalpebral reflex. The response is generally bilateral and most prominent ipsilaterally. Closure of the eyes following a painful stimulus to the face or around the eyes is referred to as a trigeminofacial reflex. A trigeminofacial reflex may be triggered by sudden airflow, warmth, or cold. A palatopalpebral reflex is the closure of the eyes in response to palatal stimulation.[9] As described, the trigeminofacial reflex is provoked by warmth, cold, and sudden air flow, and the palatopalpebral reflex is provoked by palatal stimulus. The BPR was only seen as a result of the percussion of the upper lip, so we believe that the BPR is different to the previously described trigeminofacial reflex and palatopalpebral reflex. The literature was reviewed several times, but a primitive reflex that was described as similar to BPR was not found.[1,8,10-18]

The blink reflex may be differentiated according to the neural mechanisms of the afferent pathways and the CNS. The blink reflex may also be obtained by painful stimulation of any part of the face; the severity of the stimulus should be below the pain threshold.[2] In this study, the R1, R2, and contralateral R2 latencies were found to be shorter in patients with positive BPR by supraorbital stimulation. However, the correlation between R1 response latencies was not found to be statistically significant. However, there was a statistically significant difference between the R2 and contralateral R2 latencies. The R1 response obtained from the orbicularis oculi muscle through electrical stimulation of the supraorbital nerve is the electrophysiological equivalent of oligosynaptic conduction in the mid pons. The R2 response appears as a bilateral blink reflex through stimulation of the supraorbital nerve. The R2 is a response conducted through the trigeminal spinal tract in the ipsilateral brainstem, descending in the pons, and the dorsolateral part of the medulla oblongata, reaching and crossing at the lower spinal trigeminal nucleus; it is the response of a circle of the connections of both the ipsilateral and the contralateral facial nerve motor neurons.[19] In R1, the whole reflex arc is made up trigeminal supraorbital nerve-pons and the facial nerve and limited ipsilaterally, a type of pontine segmental response. It is a reflex free of suprasegmental effects or a resistant reflex. The latency, amplitude, duration, and type of R1 are generally stable for each stimulation. Therefore, R2 is a polysynaptic reflex and it is more variable when compared with R1.[2] Cortical inhibition is probably more pronounced on R2 reflex response, which is a polysynaptic reflex, and which has a more significant relationship with the blink reflex. Latency of this response is thus expected to be shorter with disappearance of this inhibition. However, a definite explanation of these data may be difficult. Comparison of the latency difference between the earliest and latest responses for R1, R2, and contralateral R2 did not show any difference between the groups. This suggests that there was no significant difference between the groups with regards to the variability observed with response to the repeated electrical stimulus.

In the 8 patients with negative BPR, no R1 response was obtained by mental stimulation; however, 2 R2 and 2 contralateral R2 responses were obtained. In other words, the R2 response was not obtained in one of the 9 patients with positive BPR following mental stimulation, whereas R2 response was observed in only one of the 8 patients with negative BPR. The presence of a response in most BPR positive patients, and only one BPR negative patient may be important in demonstrating the difference between the 2 groups with regards to the effect of cortical inhibition. The inability to inhibit glabellar reflexes in patients with Parkinson's disease under these conditions may be explained by a decrease in threshold as is the case where only one glabella percussion elicits long lasting blinking (Myerson sign). The significant shortness of the R2 and contralateral R2 responses obtained in patients with positive BPR following supraorbital stimulation during the blink reflex supports this hypothesis.

The results of the normal individuals were similar to the patients with BPR. However, R2 and contralateral R2 responses in patients with negative BPR were a little bit shorter than the healthy subjects in supraorbital stimulation; however, this finding was not statistically significant. When the results of normal subjects in supraorbital stimulation were compared with the reflex positive group, R2 and contralateral R2 responses in the reflex positive group were shorter. This data may also support our hypothesis. Parkinson disease has a neurodegenerative progress. The similarity between the patients with negative BPR and normal subjects might be explained by the degree of neurodegeneration. Blink reflex findings might become shorter when neurodegeneration has progressed.

Tremor was observed as the dominant symptom in 5 patients with positive BPR, while bradykinesia was observed in 4 of the patients. However, tremor was the dominant symptom in all patients with negative BPR. This marked symptom difference in the clinical process may be valuable during further studies. Although the mean disease duration was longer in patients with positive BPR, no statistically significant difference was found between the 2 groups. In light of these findings, it can be suggested that there is no relationship between the clinical picture and stage of Parkinson's disease and disease duration. However, large-scale studies involving a large study population are required to further investigate this subject.

Voluntary and spontaneous movements of the extremities in patients with Parkinson's disease are typically slow (bradykinesia) and of low amplitude (hypokinesia).[20] Some studies have demonstrated that in patients with Parkinson's disease, which is associated with a deficit in these extremity movements, eye blinking was less frequently observed when compared with controls.[6] In a study where eye blinking in patients with Parkinson's disease was compared with that of controls, it was demonstrated that the rate of spontaneous eye blinking was in the range of 2-17 number of blinking movements/minute in the controls, whereas the variation was observed to involve a wider interval (range of 1-33 number of blinking movements/

minute) in patients with Parkinson's disease.[21] In another study, the rate of eye blinking movements was observed to decrease with age in both genders in patients with Parkinson's disease; however, no difference was reported between Parkinson's disease patients of more than 50 years of age and controls subjects, in respect of eye blinking movements. These results led the authors to conclude that the rate of eye blinking was not a good indicator in the evaluation of bradykinesia.[22] In our study; no statistically significant difference was found between the 2 groups. This condition may be due to the absence of any difference in both groups in respect of age and clinical stage of patients with Parkinson's disease.

The major limitation of this study was the small number of patients. Further studies that contain a larger number of patients are necessary to support the findings and hypothesis.

In conclusion, the BPR is a newly described primitive reflex in Parkinson's disease, and the hypothesis is supported by electrophysiological study.

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