ELSEVIER

AUDITORY EVENT-RELATED POTENTIALS IN PATIENTS WITH PREMATURE EJACULATION

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ABSTRACT

Objectives. To investigate in a descriptive manner the P300 component of the event-related potential (ERP), which is related to aspects of cognitive processing, in patients with premature ejaculation (PE) to determine whether there is a cognitive alteration in this condition. Recent studies with short latency evoked potentials such as cortical somatosensory evoked potentials have indicated that afferent sensory inputs from the genital area to the nervous system are increased in PE. However, the cortical neural process of ejaculation has remained poorly understood.

Methods. We performed ERPs in 20 patients with PE and in 20 age-matched healthy subjects. ERPs were evoked by an auditory oddball paradigm consisting of 150 tone bursts (80% 1 kHz; 20% 2 kHz). The latencies of the N200 and the P300 waves and the amplitude of the P300 wave were measured.

Results. The mean latencies of the N200 and P300 waves were significantly longer in the patients with PE than in the controls ($P < 0.04$ and < 0.03, respectively). No significant difference was found in the P300 amplitude between the controls and patients ($P > 0.05$).

Conclusions. These data indicate that the greater cortical representation of sensory stimuli from the genital areas that has been shown with somatosensory evoked potential studies might be related to a cognitive/neurobehavioral dysfunction. The dysfunction involves an increased time to evaluate and categorize the stimuli in the central nervous system, with no change in the quality of cognition and neural disinhibition by the prefrontal cortex to early sensory processing in subcortical or primary cortical regions, which are cognitive neural processes underlying ERP generation. UROLOGY **58:** 1025–1029, 2001. © 2001, Elsevier Science Inc.

Premature ejaculation (PE) has been defined mostly as ejaculation occurring immediately before or after vaginal intromission.[1] In the earlier reports, the etiology of this dysfunction was believed to be mainly psychological, with a few exceptional organic causes such as spinal cord injury, spinal tumor, and demyelinating diseases. The treatment strategy has primarily involved behavioral therapy and psychiatric drugs.[1,2] Recent studies with neurophysiologic tests have demonstrated that hypersensitivity of the penis and hyperexcitability of the ejaculatory center could be the bases for PE.[3–6] Stimulus-related evoked potentials such as the sacral and pudendal evoked potentials have been used in these neurophysiologic studies. However, stimulus-related evoked potentials represent an obligate neuronal response to a given stimulus and provide information about the afferent sensory functions of the neuroaxis.[7] They are independent of whether the patient is attentive to or interested in the stimulus.

Another distinct class of evoked potentials, event-related potentials (ERPs), occurs only when the subject is selectively attentive to the stimulus. Thus, ERPs have gained in popularity in the clinical context as a tool for assessing cognitive dysfunction.[8,9] The P300 test is one of the well-known ERPs. Currently, no ERP study has been done in patients with PE. The purpose of this study was to investigate whether ERP alterations exist in patients with PE in comparison with a normal control group and to point out in a descriptive manner the cognitive aspects of the disease.

MATERIAL AND METHODS

Twenty patients with primary PE ranging in age from 25 to 68 years (mean ± SD 39.9 ± 13.9) participated in the study. A

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group of 20 healthy volunteers (mean age 39.6 ± 9.8 years, range 28 to 65) served as the control subjects. PE was defined as the uncontrolled occurrence of ejaculation immediately before or in the first few minutes of vaginal penetration. Patients reporting ejaculatory latency beyond 2 minutes were excluded from the study. Other exclusion criteria for the patient group were neurologic, urologic, or systemic disorders such as alcoholism, severe hypertension, diabetes mellitus, and psychiatric disorders. The patients and controls were drug-free at least 1 week before the study. The ejaculatory latency of both the patients and the normal controls were recorded by self-report.

The P300 was recorded at the same hours of the day (between 1 and 4 PM). The patients and controls were carefully briefed about the procedure, and the auditory threshold of each subject was determined. They were asked to lie down and relax on a bed and to fix their gaze on a particular spot on the ceiling to avoid ocular artifacts and to improve their concentration during the procedure.

The P300 was recorded using the MEM-4200K evoked potential recorder (Nihon Kohden, Japan). An "oddball paradigm" of auditory stimuli was used to evoke the P300. The oddball paradigm consists of the presentation of a sequence of two different frequency tones, one of which occurs frequently (the nontarget stimulus) and the other infrequently (the target stimulus). The sequence of the target and nontarget stimuli was pseudo-random, with the constraint that no two target tones, which amounted to 20% of the stimuli presented, occurred consecutively. A 2000 Hz tone was used for the target stimulus and a 1000 Hz tone served as the nontarget stimulus. Patients and controls were instructed to keep a running mental count of the target tones. Their attention was verified by comparing the actual target tone number with the number counted by the participant. The tests were performed twice at each time and in cases of at least a 15% discrepancy between the number of delivered and counted target stimuli, the trace was rejected and the test repeated. Silver/silver chloride disc electrodes anchored with adhesive electrolyte gel were used for recording the P300. Active electrodes were placed at the Cz site of the 10-20 system referred to the linked mastoid (indifferent electrode), and the ground electrode was placed at Fz.[10] An electro-oculogram was recorded, and trials with eye movements and with electroencephalographic activity of more than 50 μv were automatically rejected. The input impedance was kept at less than 3 kilo-ohm. A high-frequency filter was set at 70 Hz and a low-frequency filter at 0.1 Hz. Alternating tone bursts, with a starting condensation phase of 10 ms rise/fall time, 100-ms duration, and intensity 70 dB greater than the normal hearing threshold at the rate of one every 2 seconds were used. Electroencephalography époques of 200 ms before and 100 ms after onset each tone were amplified and stored digitally by a computer system. At least 30 electroencephalography époques following the target tones were averaged. The task was repeated to confirm reproducibility. Long latency ERP waveforms N200 and P300 were identified. The P300 component was defined as a large positive deflection occurring 250 to 600 ms from the stimulus. The amplitude of P300 was calculated between the N200 and P300 peaks according to standard methods.

All the values are expressed as the mean ± SD, and latency values exceeding the mean ± 2.5 SD of the control group were considered abnormal. The ejaculatory latency and the parameters of ERP waveforms were statistically compared between the two groups. The unpaired Student's *t* test was used to evaluate the statistical significance of the differences, and *P* values less than 0.05 were considered statistically significant.

RESULTS

The difference in age between the patients and controls was not significantly different ($P > 0.05$). The mean ejaculatory latency of the patient and control groups was 1.0 ± 0.3 minutes (range 0.5 to 1.5) and 9.7 ± 3.6 minutes (range 5 to 20), respectively. The difference in the ejaculatory latency between the two groups was significant ($P < 0.05$). Well-formed and reproducible waveforms were elicited from both the control subjects and the patients (Figs. 1 and 2). The mean P300 latency in the control and patient groups was 315.9 ± 32.1 ms and 341.0 ± 33.9 ms, respectively (Table I). Two patients had a P300 latency value exceeding the upper limits of normal (mean ± 2.5 SD). The difference in the P300 latency between the two groups was statistically significant ($P < 0.05$). The mean N200 latency in the patients was significantly longer than that in the control group ($P < 0.05$). No significant difference in the P300 amplitude was found between the controls and patients.

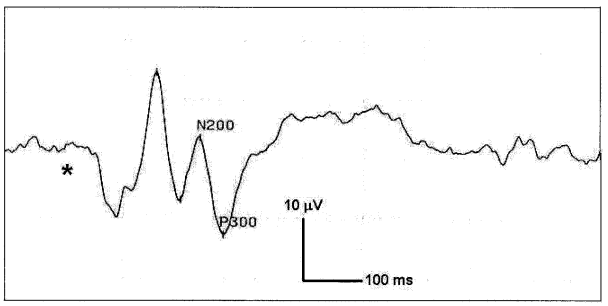

FIGURE 1. *Representative responses to target tones obtained from one of the controls. Asterisk represents the onset of amplification and recording 100 ms after the tonal stimulus.*

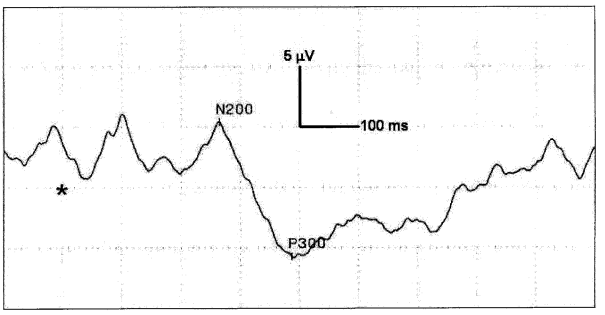

FIGURE 2. *Representative responses to target tones obtained from one of the patients who had a P300 latency value (390 ms) exceeding the upper limits of normal. Asterisk represents the onset of amplification and recording 100 ms after the tonal stimulus.*

COMMENT

Although the cause for PE is believed to be primarily psychological, the results of some studies with neurophysiologic testing suggest a neurologic basis. These studies, including penile biothesiom-

TABLE I. *Age, ejaculatory latency, N200 and P300 mean latency, and P300 amplitude values in patients and controls*

	Patients (n = 20)	Controls (n = 20)	*P* Value
Age (yr)	39.9 ± 13.9 (23–68)	39.6 ± 9.8 (28–65)	0.90
Ejaculatory latency (min)	1.0 ± 0.3 (0.5–1.5)	9.7 ± 3.6 (5–20)	0.00
N200 latency (ms)	240.1 ± 18.4 (208–280)	225.0 ± 24.6 (186–270)	0.04
P300 latency (ms)	341.0 ± 33.9 (286–406)	315.9 ± 32.1 (264–361)	0.03
P300 amplitude (μV)	12.7 ± 5.7 (4.6–23.3)	13.1 ± 8.2 (4.0–25.6)	0.80

etry, sacral evoked response, and pudendal somatosensory evoked potential tests, essentially evaluate the somatic afferent pathway.[3–6,11] Beginning with the sensory afferent system, decreased penile receptor thresholds in patients with PE have been shown, although contradictory evidence surrounds this issue.[4,11,12] Colpi *et al.*[3] have found differences in sacral evoked potentials between patients with PE and controls, suggesting a hyperexcitability of the bulbocavernous reflex that can be explained by an increased sensory input to the sacral spinal segments.

Different genital areas, such as the clitoris, penile shaft, glans penis, or perineum, have been used to test pudendal somatosensory evoked potentials.[7,13,14] The studies concerning neurophysiologic abnormalities in patients with PE are few in number, and most have been performed in small groups of patients and have not been confirmed. However, most investigators have found similar results, including the presence of a higher amplitude and/or shorter latency of pudendal somatosensory evoked potentials measured by stimuli applied at different genital areas in patients with PE. They have also suggested a greater cortical representation, in other words, augmentation, of the sensory stimuli from the genital areas.[3–5] Therefore, when these findings were considered, the excessive neural stimuli induced by the hypersensitivity and hyperexcitability of the genital areas have been thought to cause uncontrolled ejaculation. Nevertheless, the level of neuroaxis responsible for the hyperexcitable state of patients with PE—whether the receptor level, sacral/suprasacral spinal level, or central nervous system level involving several inhibitory mechanisms—has not been delineated.

Several studies that investigated the effects of therapeutic agents such as a topical agent or antidepressant drugs on the pudendal somatosensory evoked potentials in patients with PE have given different results. Xin *et al.*[15] reported that the mean latency of the pudendal somatosensory evoked potentials after the application of the topical SS cream was longer than before the application. In opposition to these findings, most investigators have reported that the latency of the pudendal somatosensory evoked potentials did not change with the treatment of antidepressant drug therapy.[4,11]

Although several studies about the afferent sensory pathway in patients with PE have been done, the cortical neural processes of ejaculation that might be related to the behavioral aspects have remained poorly understood. A study with single photon emission tomography in healthy men during orgasm showed a decrease in the cerebral regional blood flow during orgasm in all areas, except in the right prefrontal cortex, where the cerebral regional blood flow increased significantly.[16] It is accepted that the dorsolateral prefrontal cortex is crucial for the control of sustained and phasic attention to environmental events.[17] A single study reported a net inhibitory output to the subcortical regions from the prefrontal cortex. This prefrontal-subcortical inhibitory system provides a potential mechanism for the suppression of the irrelevant sensory inputs at an early stage of afferent sensory processing to create a noiseless cognitive milieu for the relevant sensory input.[18,19] ERPs are voltage fluctuations in the scalp electroencephalogram that occur in response to task-relevant stimuli and can be extracted from the ongoing electroencephalography using averaging method. In the recent theories centered on the generation of ERPs, P300 reflect the serial and parallel activation of multiple neocortical and limbic regions related to the attention and working memory mechanisms.[20]

In addition to organic causes of cognitive disorders, such as dementia, showing longer latency and decreased amplitude of P300, ERP alterations have also been reported in subjects with various neurobehavioral syndromes.[9] In narcolepsy, prolonged P300 latency has been reported, and research with alcoholism, antisocial personality disorder, schizotypal personality disorder, panic disorder, anxiety disorders, and obsessive-compulsive disorder have demonstrated P300 alterations, such as amplitude reductions, latency increments, and/or topographic differences compared with controls.[21–28]

The latency of the P300 has been suggested to measure the stimulus evaluation time concerning

the central nervous system, and the amplitude has been related to the allocation of the neural resources, efficiency of the cognitive processing, the certainty of decision, and target probability.[29] Although the clinical meaning of the N200 is less clear than that of P300, the latency of the N200 has been suggested to measure the effort of stimulus categorization.[30]

The present study, which is the first investigation of ERP in patients with PE, showed that the mean latencies of the N200 and P300 were significantly increased in the patients compared with the controls. Increased N200 and P300 latencies in patients with PE might be related to increased categorization and evaluation time of stimulus. Therefore, when considered in the light of pudendal somatosensory evoked potential studies showing the hyperexcitable state of patients with PE, the greater cortical representation of the sensory stimuli from the genital areas might be related to this stimulus evaluation dysfunction and neural disinhibitions by the prefrontal cortex on early sensory processing in subcortical or primary cortical regions, as shown by the longer latencies of N200 and P300. The absence of amplitude difference might be because patients with PE probably have no alterations in the quality of cognitive processing. However, ERP studies topographically evaluating both hemispheres and functional imaging studies are needed to clearly demonstrate the cognitive processing in patients with PE.

CONCLUSIONS

The results of the present study showed that the latencies of the N200 and the P300 components of the ERP in patients with PE are significantly longer than those in the controls, without any change in the amplitude of the ERP. These findings suggest that there might be an increased duration to evaluate and categorize the sensory stimuli in the central nervous system without any change in the quality of cognitive processing in patients with PE. Therefore, it seems necessary to evaluate the central nervous system component of such patients using ERPs and/or functional imaging studies in addition to the evaluation of the afferent sensory system.

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