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Topographic Abnormalities in Event-Related Potentials in Children With Monosyptomatic Nocturnal Enuresis

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Aims: A functional maturational delay in the central nervous system is dwelled upon in the pathogenesis of monosymptomatic nocturnal enuresis (MNE). In this study we studied whether according to controls N200 and P300, components of the event-related potential (ERP), which is related to aspects of cognitive processing, showed any difference in its topographic distribution in children within the age group 10–13 with monosymptomatic nocturnal enuresis and discussed its relation to the pathogenesis of MNE. **Methods:** We performed P300 in 18 patients with MNE and in 16 age-matched healthy subjects. P300 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:** There was no statistical difference between the enuretic group and the controls in N200 and P300 latency and amplitude in the midline frontal (Fz), central (Cz), and parietal (Pz) recording site of the 10–20 International System. In the enuretic group while P300 amplitude in the Fz site was significantly less than the P300 amplitude in the Cz site, there was no statistical difference between the Fz and Pz P300 amplitude values. **Conclusions:** When different levels of maturational delay are considered in MNE, it may be claimed that maturational delay in children whose enuresis lasts until older ages will be different from those whose enuresis ends at an early age. The determination of P300 amplitude in parietal records being less in enuretics when compared to the controls may show that there are regional differences in stimuli processing rate/quality. *Neurourol. Urodynam. 23:237–240, 2004.* © 2004 Wiley-Liss, Inc.

Key words: enuresis nocturna; event-related potential; P 300 topography

INTRODUCTION

Monosymptomatic nocturnal enuresis (MNE) is characterized by bed-wetting after the age of 5 [Koff and Jayanthi, 2002]. Urinary incontinence in the daytime and/or other urinary symptoms are not found in MNE. A functional maturational delay in the central nervous system is dwelled upon in the pathogenesis of MNE [Norgaard et al., 1998]. Koff has suggested that maturational delay in the central nervous system in nocturnal enuresis may occur in both afferent and efferent CNS limbs [Koff, 1996]. The first of these is afferent neuronal developmental delay. This means, during sleep, the central nervous system mechanisms lack awareness of signals concerned with over-full bladder and contractions and results in the child's inability to wake up. Related to efferent neuronal developmental delay, the child is unable to prevent micturition during sleep. Koff indicates that unawareness of the signal or the inability to restrain the reflex are not enough reasons alone for bed-wetting. Bladder contractions during sleep should be existent and the child should still not be able to wake up even in the existence of these contractions.

Sleeping studies and the research on the inhibition of arousal reflex performed on enuretic children, have suggested that there may be a failure in the reticulo-thalamic structures [Kawauchi et al., 1998; Ornitz et al., 1999; Kohyama et al., 2000; Ornitz et al., 2000; Yamao et al., 2000; Wolfish, 2001]. Iscan et al. [2002] have related the P300 latency delay of event-related endogen potential in enuretic children to thalamic structures. These researchers also indicate that P300 also shows certain topographic differences related to age groups. In this study, we studied whether compared to controls P300 and N200, components of the event-related potential which is related to aspects of cognitive processing showed any difference in its topographic distribution in children within the age group 10–13 with monosymptomatic nocturnal enuresis and discussed its relation to the pathogenesis of "MNE."

MATERIALS AND METHODS

Patients and Health Controls

The study was performed on patients who were admitted in Turgut Ozal Medical Centre Pediatric Urology Polyclinic

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between January 2000 and 2002 with a complaint of enuresis and who had been diagnosed as monosymptomatic enuresis nocturna according to DSM IV diagnosis criteria [American Psychiatric Association, 1994]. In the result of psychiatric evaluation, those who had received an additional psychiatric diagnosis along with primary nocturnal enuresis, a history of mental retardation and head trauma were excluded. A series of controls and tests were performed in all cases in order to discriminate organic causes as well as other causes of enuresis. These were detailed physical examination, full blood tests, full urine tests, uroflowmetric examination, stool microscopy, ultrasonographic examination of the urinary system, and pyelography when necessary.

A total of 18 patients having 10–30 wet nights per month (average 23.1 ±7.7 nights) out of which 13 were boys and 5 girls, whose age ranged between 10 and 13 years with monosymptomatic nocturnal enuresis, and a total of 16 healthy children (9 boys, 7 girls), with an age range of 10–13 years were included in the study.

There was no statistically meaningful difference between the patient and control groups in terms of age, sex, and education.

P300 Recording

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 MEB-4200K evoked potential recorder (Nihon Kohden, Tokyo 161, 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 2,000 Hz tone was used for the target stimulus and a 1,000 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 in the midline frontal (Fz), central (Cz), and parietal (Pz) recording site of the 10–20 International System, referred to the linked mastoid (indifferent electrode). 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 kΩ. 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 msec rise/fall time, 100-msec duration, and intensity 70 dB greater than the normal hearing threshold at the rate of one every 2 sec were used. Electroencephalography epochs of 200 msec before and 100 msec after onset each tone were amplified and stored digitally by a computer system. At least 30 electroencephalography epochs 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 250–600 msec 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.

Statistical Analysis

SPSS 10.0 for Windows was used in computing statistics. The statistical evaluations of data were made by one way analysis of variance (ANOVA) for comparison between means, by unpaired *t*-test, by Fisher's exact test, by Wilcoxon Rank Sum test, appropriately. P values <0.05 were considered statistically significant.

RESULTS

There was no statistical difference between the enuretic group and the controls in terms of age and sex (Table I). N200 latency and P300 latency in the Fz, Cz, Pz recording site, were not statistically different in the enuretics from the control group. While the P300 amplitude of the patients and controls in the Fz and Cz recording site was not statistically different, in the Pz recordings the P300 amplitude of the enuretics was found significantly less than the controls.

In the Fz recordings, the P300 amplitude was significantly less ($P < 0.05$, $P < 0.02$, respectively) in the control group when compared to the Cz and Pz recordings. In the enuretic group while P300 amplitude in the Fz site was significantly less than the P300 amplitude in the Cz site ($P < 0.005$), there was no statistical difference between the Fz and Pz P300 amplitude values (Table II).

In the patient and control groups, there was no statistical difference between N200 and P300 latencies of the potentials recorded in the Fz, Cz, and Pz sites.

DISCUSSION

A number of theories have been proposed to explain why children with MNE fail to recognize or respond to their full or contracting bladder during sleep. Although these theories

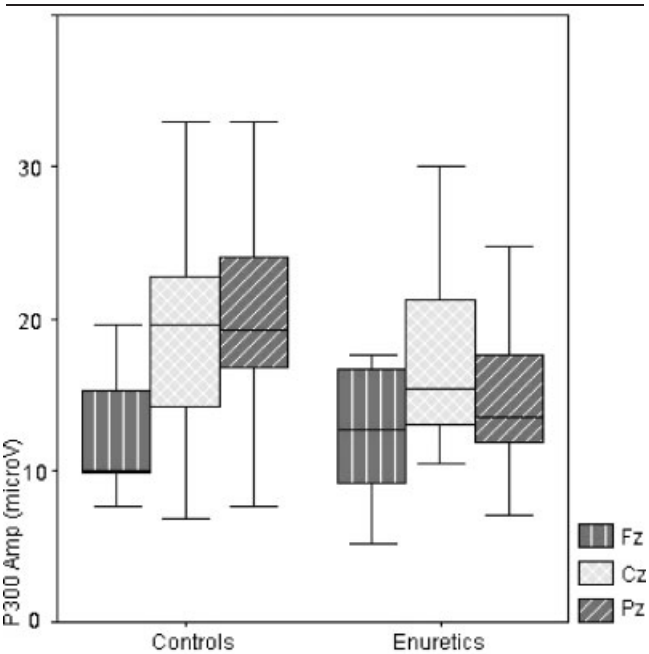
TABLE I. Age, Sex, P300 Latency and Amplitude Values in Patients and Controls

		Controls (n:16)	Patients (n:18)	*P*
Sex	Male/female	9/7	13/5	NS
Age		11.9 ± 1.1	11.3 ± 1.1	NS
	N200 latency (msn)	246.3 ± 17.7	254.5 ± 26.0	NS
	P300 latency (msn)	326.5 ± 30.1	341.4 ± 21.3	NS
Fz	P300 amplitude (μV)	13.7 ± 7.3	13.3 ± 6.1	NS
	N200 latency (msn)	249.3 ± 32.3	250.9 ± 19.4	NS
	P300 latency (msn)	338.1 ± 29.6	349.0 ± 35.2	NS
Cz	P300 amplitude (μV)	18.5 ± 7.1	17.5 ± 6.0	NS
	N200 latency (msn)	242.0 ± 21.9	243.1 ± 24.3	NS
	P300 latency (msn)	334.3 ± 42.9	353.3 ± 42.6	NS
Pz	P300 amplitude (μV)	19.6 ± 6.7	15.2 ± 5.7	0.03

NS, not significant.

are diverse and may be able to explain selected cases, there is no single explanation for this symptom, and in each individual multiple factors may be operative [Koff and Jayanthi, 2002]. But the lack of success of desmopressin treatment in all enuretic children caused the questioning of the unitary approach to pathogenesis [Koff, 1996]. Even though maturational delay is the most considered approach in the pathogenesis of MNE, there are many different evidences concerning the level of maturational delay and its extensiveness which are contradictory or inconsistent. Various abnormalities in children with enuresis nocturna, such as reduced bladder capacity, detrusor overactivity, or insufficiency in the circadien rhythm of the vasopressin, have been reported [Yeung et al., 1999; Natochin and Kuznetsova, 2000; Kawauchi et al., 2002]. Leaving aside these abnormalities, it is indicated that even maturational delay in the neuronal circuit related to micturition control in children with enuresis cannot be explained in only one way. In various studies, hypoexcitability in the sacral sphincteric nucleus of enuretic children, arousal response differences when compared to normal children and pontine inhibitor circuit differences have been presented and the relation of these neurophsyiologic findings to micturition control have been discussed [Podnar et al., 1997; Kawauchi et al., 1998; Yamao et al., 2000; Wolfish, 2001]. Iscan et al. [2002] as a result of the P300 test which is another neurophysiological test used in the evaluation of cognitive functions, have reported that they have determined a latency delay in the middle (Cz) and back (Pz) recording sites of the head in enuretic children when compared to the control group. The authors have suggested that P300 latency delay may an evidence of a functional maturational delay in the talamus.

TABLE II. P300 Amplitude Difference in the Fz, Cz, Pz Recording Sites in Patients and Controls



The N200 component of the event-related potentials is accepted to be related with the determination of the mismatch in stimulus flow [Oken, 1987]. The automatic determination of the mismatch in stimulus flow is considered to be related to mismatch negativity, determination with conscious judgement to be related to N2b [Goodin, 1992]. The P300 component is accepted to reflect the process of accurate and clear evaluation of stimuli. That is, in a cognitive process in which P300 generate, the information about the existing condition is stored in a memory process in order of readiness for future events (working memory process) and the context is revised (context updating) [Knight, 1997; Knight and Scabini, 1998].

In our P300 study, we performed on the 10–13 age group, we did not determine a difference in latency between the enuretic children and the control group. According to the control, the indifference in N200 and P300 latency aroused the thought that in enuretics of this age group there is no difference between the determination of stimulant differences and the evaluation speed of the stimulant.

In another finding, Iscan et al. [2002] have determined in their study is that enuretics have different findings for each age group. They have indicated that the latency and amplitude recordings of the Cz region were different when compared to

the Pz region records in the age 9 group of enuretics and that they had not determined such a finding in smaller age groups. In our study, we have also found the P300 amplitude to be less in the posterior (Pz) region in age 10 and above enuretic children according to the controls. In the controls, there was a statistically significant amplitude difference between the anterior and posterior recording regions of the head. This differencewas not seen in the enuretic group.

While MNE is seen at a rate of 15% in the 5-year-old boys, as the age increases the frequency of enuresis decreases and it is known that the decrease reaches to 1% at the age of 15. Koff claims that enuresis is caused by a delay in maturation in afferent and efferent neuronal tractus, and as maturation completes the symptoms disappear. When different levels of maturational delay are considered in MNE, it may be claimed that maturational delay in children whose enuresis lasts until older ages will be different from those whose enuresis ends at an early age. In other words, it can be stated that maturational delay in MNE ending at an early age will be different and at lower levels than those who end at a later age. When the results of the two studies, one being ours and the other by Iscan et al. [2002], searching for P300 disorder in enuretics are compared, even though the design and case choices of the two studies are different, they both show that P300 abnormality patterns change in enuretic children as the age increases.

The determination of P300 amplitude in parietal records being less in enuretics when compared to the controls may show that there are regional differences in stimuli processing rate/quality. P300 studies performed with the broader grouping of enuretics according to age and sex may give more clear information on the electrophysiologic differences of cognitive function in these patients.

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