Brainstem Auditory-Evoked Potentials in Children with Primary Nocturnal Enuresis

Primer Enürezis Nokturnalı Çocuklarda Beyin Sapı İşitsel-Uyarılmış Potansiyelleri

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ABSTRACT Objective: Primary nocturnal enuresis (PNE) is a developmental disorder. It is characterized by involuntary micturating over 5 years of age. The main etiopathogenetic causes are genetic and physiologic factors, sleep abnormalities, autonomic nervous system dysfunction and developmental delay. PNE was reported to be related to functional immaturity of the central nervous system. The control centers for bladder function and micturation are localized at pons. However, studies investigating the pons regarding this function are few. In this study, brainstem functions were evaluated with brainstem auditory-evoked potential (BAEP) in children with PNE. **Material and Methods:** Forty children [18 girls and 22 boys; mean age 7.8±2.9 years (range 5.5-10.5)] with PNE (Group I) and 40 healthy children [18 girls, 22 boys, mean age 7.5±3.2 years (range 5.5-10)] (Group II), were enrolled in this study. The cases with mental retardation, neurological disorders, metabolic diseases, psychiatric abnormality (attention deficit/hyperactivity syndrome), and urinary tract disorders were excluded. **Results:** Though statistically insignificant, the peak and interpeak latency values in Group I were longer than in Group II. **Conclusion:** PNE is a common entity of childhood with an incompletely defined pathogenesis. Maturational delay of the central nervous system has recently been noticed in the etiology. However, due to the controversial results, we suggest that further studies with larger sample sizes and new methods are required.

Key Words: Nocturnal enuresis; etiology; evoked potentials, auditory, brain stem

ÖZET Amaç: Primer noktürnal enürezis (PNE) gelişimsel bir bozukluktur ve 5 yaşın üzerinde istemsiz işeme ile karakterizedir. Etiyopatogenezinde genetik ve fizyolojik faktörler, uyku bozuklukları, otonom sinir sistemi fonksiyon bozukluğu ve gelişme geriliği vardır. PNE'nin santral sinir sisteminin fonksiyonel gelişmemişliği ile ilişkili göründüğü bildirilmiştir. Mesane fonksiyonu ve işeme kontrol merkezleri ponsta yerleşmiştir. Ancak, bu konuda pons ile ilgili araştırmalar azdır. Bu çalışmada, PNE'li çocukların beyin sapı fonksiyonları, beyin sapı işitsel-uyarılmış potansiyelleri (BSİP) ile değerlendirildi. **Gereç ve Yöntemler:** PNE'li 40 çocuk [18 kız ve 22 erkek, yaş ortalaması 7,8±2,9 yıl (aralık 5,5-10,5)] (Grup I) ve 40 sağlıklı çocuk [18 kız, 22 erkek, yaş ortalaması 7,5±3,2 yıl (aralık 5,5-10)] (Grup II) çalışmaya alındı. Zekâ geriliği, nörolojik bozukluklar, metabolik hastalıklar, psikiyatrik bozukluk (dikkat eksikliği/hiperaktivite sendromu) ve idrar yolu hastalıkları gibi durumları olan olgular çalışmadan dışlandı. **Bulgular:** İstatistiksel olarak anlamlı olmasa da, Grup I'in tepe ve interpik latans değerleri Grup II'nin değerlerinden uzundu. **Sonuç:** PNE eksik tanımlanmış patogenezi ile çocukluk çağının sık görülen bir tablosudur. Son zamanlarda etiyolojisinde, merkezi sinir sisteminin olgunlaşmasında gecikme olmasının rol oynadığı not edilmiştir. Ancak, bu çalışmaların kesin olmayan sonuçları nedeniyle, daha geniş çaplı ve yeni yöntemler ile yapılmış daha fazla çalışmalara gerek olduğunu düşünüyoruz.

Anahtar Kelimeler: Gece idrar kaçırma; etiyoloji; uyarılmış potansiyeller, işitsel, beyin sapı

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Enuresis is defined as repeated, spontaneous voiding of urine during sleep in children at the age of five years or older. Enuresis may be classified as primary or secondary, and monosymptomatic (uncom-

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plicated) or polysymptomatic (i.e., concominant lower urinary tract symptoms are present). Monosymptomatic children with primary nocturnal enuresis (PNE) have no lower urinary tract symptoms other than nocturia, and no history of bladder dysfunction.[1-3] According to International Children's Continence Society (ICCS), primary enuresis is defined as a child who has previously been dry for less than 6 months.[4]

Primary nocturnal enuresis is three times more common than daytime wetting and affects 6.7 percent of younger children and 2.8 percent of older children.[2,3]

PNE is caused by disparity between bladder capacity and nocturnal urine production and the child's failure to awaken in response to a full bladder. Recent research has established three major pathogenetic mechanisms as crucial, including nocturnal polyuria, detrusor overactivity and an increased arousal thereshold. Since neither the polyuria mechanism nor nocturnal detrusor overactivity explain why the children do not awaken, sleep mechanisms must also be involved. Enuresis tends to disappear spontaneously as the child grows due to the maturation of the central nervous system.[5] PNE was reported to be related to functional immaturity of the central nervous system. The control centers for bladder function and micturation are localized at the pons.[6] However, there are few investigational approaches including pons with regard to this function. In this study, brainstem functions were evaluated with brainstem auditory-evoked potential (BAEP) in children with PNE.

MATERIAL AND METHODS

Forty children [18 girls and 22 boys, mean age 7.8±2.9 9 years (range 5.5-10.5)], with PNE (Group I) and 40 healthy children, [18 girls and 22 boys, mean age 7.5±3.2 years (range 5.5-10)] (Group II) were enrolled in the study. In addition, cases in Group I were divided into two subgroups as Group **Ia** (5.5-8 years, 14 patients) and Group Ib (8-10.5 years, 26 patients). Similarly, the control group was divided into Group IIa (5.5-8 years, 15 children) and Group IIb (8-10 years, 25 children). The cases with mental retardation, neurological disorders, metabolic diseases, psychiatric abnormality (attention deficit/hyperactivity syndrome), and urinary tract disorders were excluded. Developmental history (head control, sitting with support, sitting without support, crawling, walking, speaking) was obtained from parents in patient and control groups.

BAEP measurements were performed in both groups for one time. In all cases, a complete ear and hearing examination was performed prior to the initiation of the study to exclude any outer and middle ear pathologies. The potentials were recorded as described in detail. BAEP measurements were performed without any pharmacological sedation after feeding during spontaneous sleep. The BAEP was recorded with an Eosate Biomedica System. Electrodes were attached to the mastoid processes (reference electrode), vertex (active electrode) and midline forehead (ground electrode). The disc electrodes were used for recording. Stimulation was given by tube earphone. The auditory click stimuli were 11.4/s. The clicks were given at intensities up to 90 dB hearing level and 200 repetitions were recorded for each ear. Absolute latency for waves I, III, V and interpeak latency I-III, III-V and I-V were recorded. Latency values obtained for left and right ears were averaged to represent one value in each case.

All statistical analyses were performed by SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as median (min.-max.). Differences between the study group and the control group were compared by Mann-Whitney U test. A level of $p<0.05$ was considered statistically significant.

The study was performed with the approval of the local ethics committee, and informed consents were obtained from the parents.

RESULTS

There were no differences between the two groups in terms of age variables ($p=0.268$). Though statistically insignificant, the median peak and interpeak latency values in Group I were longer than in Group II. Results were shown in Table 1. No difference was noted between Group Ia and Group IIa

in terms of BAEP (Table 2). Similarly, there was no significant difference between Group Ib and Group IIb (Table 3). In addition, no difference was found between enuretic patients and controls in terms of developmental stages (Table 4).

DISCUSSION

Enuresis is a common problem among children and adolescents, and can lead to important social and psychological disturbances. In our country, Göv et al. showed that enuresis was associated with raising anxiety in schoolchildren.[7] However, the complete etiopathogenesis of the disease is still unknown. The etiology of enuresis is multi-factorial, with maturational delay of the central nervous system and psychosocial factors being prominent factors.[1-5] Several studies have shown that a large proportion of enuretic children have a deranged circadian rhythm of antidiuretic hormone secretion that results in nocturnal polyuria.[8]

Jarvelin MR et al. showed relative nocturnal polyuria due to insufficient antidiuretic hormone release during nocturnal sleep.[9]

According to Barone et al., obstructive sleep apnea is a relatively common pediatric condition, and it may be associated with primary nocturnal enuresis.[10] On the other hand, as suggested by Güven et al.,[11] the increased prevalence of obesity

TABLE 1: Brain auditory-evoked potential of Group I (enuretic patients) and Group II (control).*

Absolute wave latency and interpeak latency	Group I (n= 40)	Group II (n= 40)	p values
Latency I (msec)	2.12 (1.86-3.20)	1.92 (1.78-3.00)	0.174
Latency III (msec)	4.60 (3.42-5.92)	4.10 (3.32-5.40)	0.306
Latency V (msec)	6.26 (5.40-6.80)	5.92 (5.42-6.40)	0.198
Interpeak latency I-III(msec)	2.42 (1.92-3.10)	2.20 (1.88-2.92)	0.266
Interpeak latency III-V(msec)	2.20 (1.82-2.72)	1.98 (1.68-2.74)	0.176
Interpeak latency I-V(msec)	4.10 (3.48-4.68)	4.08 (3.86-4.48)	0.190

*Values (msec) are given as median- (min.-max.).

TABLE 2: Brain auditory-evoked potential of the Group Ia and Group IIa.

Absolute wave latency and interpeak latency	Group Ia (n= 14)	Group IIa (n= 15)	p values
Latency I (msec)	2.98 (2.38-3.20)	2.35 (1.98-3.00)	0.118
Latency III (msec)	5.02 (4.18-5.92)	4.45 (3.88-5.40)	0.096
Latency V (msec)	6.38 (5.44-6.80)	5.98 (5.50-6.40)	0.215
Interpeak latency I-III(msec)	268 (2.0-3.10)	2.40 (1.98-2.92)	0.302
Interpeak latency III-V(msec)	2.30 (1.82-2.52)	2.02 (1.80-2.74)	0.116
Interpeak latency I-V(msec)	4.30 (3.88-4.68)	4.28 (4.00-4.48)	0.468

TABLE 3: Brain auditory-evoked potential of Group Ib and Group IIb.

Absolute wave latency and interpeak latency	Group Ib (n= 26)	Group IIb (n= 25)	p values
Latency I (msec)	1.98 (1.86-3.02)	1.82 (1.78-2.86)	0.228
Latency III (msec)	4.15 (3.42-5.06)	3.76 (3.18-4.56)	0.114
Latency V (msec)	5.88 (5.40-6.10)	5.34 (5.42-5.96)	0.366
Interpeak latency I-III(msec)	1.98 (1.92-2.64)	1.92 (1.88-2.56)	0.385
Interpeak latency III-V(msec)	2.16 (1.85-2.72)	2.10 (1.68-2.55)	0.316
Interpeak latency I-V(msec)	3.62 (3.48-3.90)	3.84 (3.86-3.95)	0.416

TABLE 4: Developmental stages of enuretic children and control groups.

	Group I	Group II	p values
Head Control	2.2 months	2.2 months	NS*
Sitting with support	4.5 months	4.4 months	NS
Sitting without support	6.1 months	6.2 months	NS
Crawling	8.5 months	8.5 months	NS
Walking	12.5 months	12.4 months	NS
Speaking	11.9 months	11.9 months	NS

*NS= Not significant.

reported in children with PNE is attributable to obstructive sleep apnea.

Heredity is one of the most important factors contributing to enuresis. While only 15% of the children had no family history of enuresis, it increased to 44% when one of the parents used to wet his/her bed and to 77% when both parents did. The probability of having enuresis increases as a function of the closeness and number of blood relatives with history of enuresis.[12]

Pathophysiological findings suggest another main factor, which is the patient's inability to wake up in response to signals from a full bladder.[13] Therefore, recent studies have looked more closely at the involvement of the central nervous system in the cause of PNE. The region of interest has been hypothesized to lie within a tiny area surrounding the vicinity of the pontine micturation center. Enuretic children were shown to be more difficult to arouse than age-matched controls. The arousal inability in patients with nocturnal enuresis may relate to either elevated arousal thresholds or the presence of spontaneous uninhibited bladder functions.[5,14]

As a result, increasing proportions of patients improved with age highlights the occurrence of maturational delay of the central nervous system. Hallioğlu et al. evaluated the maturation of the central nervous system with visual and quantitative electroencephalography (EEG).[15] They concluded that insufficient cerebral maturation was an important factor in the pathogenesis of PNE. Kohyama et al. proposed that enuretic patients had dysfunctions in the pontine reticular formation.[6] Iscan et al. studied the central nervous system function involvement in nocturnal enuresis.[16] P300 and N200 event-related brain potentials and brainstem auditory-evoked potentials were assessed in 35 enuretic children at the ages of seven to nine. According to their results, longer P300 latency in enuretic children compared to non-enuretics is an evidence of maturational delay of the central nervous system functioning. Similar to the results of those studies, children with PNE showed a slower motor performance than healthy children did, particularly for repetitive hand and finger movements. This study provides evidence for a maturational deficit in motor performance in children with PNE. In addition to a maturational deficit of the brainstem, it is suggested that there is a possible maturational deficit of the motor cortex circuitry and related cortical areas in children with PNE.[17]

In our study, mean peak and interpeak latencies were longer in the enuretic group than in the control group, but this difference was statistically insignificant.These results are not different from the results of the previous study, which were also not significant. Our study also showed that mental and motor development of enuretic children was similar to age-matched healthy controls like BAEP measurements. It is considered that enuretic children do not have major motor and mental handicaps and pathogenesis may be related to the maturation of the nervous system.

Consequently, PNE is a common entity of childhood with an incompletely defined pathogenesis. Currently, nocturnal low bladder capacity and detrusor overactivity, nocturnal polyuria and increased arousal thereshold are the leading pathogenetic mechanisms. Maturational delay of the central nervous system has recently been noticed as a cause in the etiology. However, due to the controversial results, we suggest that further large-scale studies using new methods are essential.

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