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Hyperventilation Response in the Electroencephalogram and Psychiatric Problems in Children with Primary Monosymptomatic Nocturnal Enuresis

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Objectives: The aim of this study was to determine the frequency of an increased hyperventilation (HV) response in the electroencephalogram and to compare the results of psychometric assessments and electroencephalography (EEG) patterns in children with and without primary monosymptomatic nocturnal enuresis and in dry siblings of enuretics. We also compared the results of psychometric assessments and EEG patterns between enuretic and non-enuretic children.
Material and Methods: The study included 89 children divided into three groups: 41 with primary monosymptomatic nocturnal enuresis, their 29 dry siblings and 19 with no history of voiding dysfunction (controls). Resting EEG changes were evaluated in all children. In addition to a psychiatric evaluation, the Maudsley Obsessive Compulsive Questionnaire, the Beck Child Depression Inventory and the State and Trait Anxiety Inventory for Children were used to assess obsessive—compulsive disorder, depression and anxiety, respectively.
Results: The time at which real words were first spoken occurred significantly later in enuretic children ($p < 0.01$). The frequency of EEG abnormalities was significantly higher in the enuresis group and in their dry siblings than in the control group ($p < 0.01$). Additionally, as an indicator of cortical dysmaturity, an increased HV response was observed more often in enuretic children and their dry siblings than in the control group ($p < 0.001$). Anxiety scores for the enuretic children were higher than those for the controls ($p < 0.01$). There was no significant difference in psychiatric problems between the enuresis and control groups ($p > 0.05$).
Conclusions: The increased frequency of a high-level HV response in resting-state EEG recordings and the anxiety scores suggested that delayed cortical maturity and high anxiety may be important factors in the pathogenesis of primary monosymptomatic nocturnal enuresis. The HV responses in the dry siblings of the enuretic children may emphasize the relationship between insufficient cerebral maturation and the genetic origin of nocturnal enuresis.

Key words: dry siblings, electroencephalography, hyperventilation response, psychiatric problems, primary monosymptomatic nocturnal enuresis.

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Nocturnal enuresis is defined as the involuntary voiding of urine in bed beyond the age at which bladder control is normally expected (1). The incidence of primary nocturnal enuresis is 20% in children aged 5 years, 11.5% in children aged 7–12 years and 1–2% even in adolescents (2, 3). The etiology seems to be multifactorial and several factors have been described to explain this phenomenon, including delayed maturation of the nervous system controlling bladder function, genetic influences, difficulties in waking, decreased night-time secretion of antidiuretic hormone and stress and psychologic factors (4, 5).

Nocturnal enuresis in the pediatric age group can create tremendous anxiety for both children and parents because it interferes with socialization (6, 7). Owing to the social consequences of this phenomenon, a large proportion of affected patients seek medical attention.

More recently, the hypothesis that enuresis represents delayed functional maturation of the central nervous system (CNS) has become attractive in this multifactorial model (8). It has been demonstrated that some enuretic children have some neurological symptoms (9, 10); however, there is little actual evidence of maturational delay or damage to the nervous system. Regarding the maturation of the CNS, a limited number of electroencephalography (EEG) studies were designed to clarify the relationship between nocturnal enuresis and selective cortical dysmaturity. On the other hand, the hyperventilation (HV) response is

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commonly considered to be a sign of brain damage or dysfunction or instability of the cerebral cortex as a result of delayed maturation (11, 12). This phenomenon consists of shorter or larger runs of regular, sinuous, slow waves of high amplitude and of a frequency of 2.5–3.5 sec, which are usually maximal over the posterior head regions, in response to forced breathing.

The aim of this study was to determine the frequency of an increased HV response in the electroencephalogram in children with and without primary monosymptomatic nocturnal enuresis and in the dry siblings of the enuretics. We also compared the results of psychometric assessments and EEG patterns between enuretic and non-enuretic children.

MATERIAL AND METHODS

Study design

The study included 89 children (6–16 years old) divided into three groups: those with primary monosymptomatic nocturnal enuresis (enuretic group; $n = 41$); the dry siblings of the children with enuresis (sibling group; $n = 29$); and children with no history of voiding dysfunction (control group; $n = 19$). Children who had never been dry at night for an uninterrupted period of at least 6 months were classified in the enuretic group (13). All parents and children were asked to participate in the study after being informed about the necessity of the investigations and methods. The institutional ethical committee approved the study. Detailed psychiatric interviews and psychological assessments, neurological and urological examinations were performed. Perinatal histories of all children were obtained from hospital records. Children with causes of secondary enuresis and EEG disturbances including neurogenic bladder and associated spinal cord abnormalities, urinary tract infections, posterior urethral valves in boys and an ectopic ureter in girls, seizure disorders, CNS infections, cerebrovascular disorders, cranial trauma, any chronic drug usage, any known metabolic diseases (e.g. diabetes mellitus), prominent mental retardation or taking of any medication containing psychotropic drugs were excluded from the study.

EEG recordings

Resting-state EEG recordings were performed in all of the subjects who had been referred after neuropsychiatric and urological evaluations. Twelve-channel digital EEG recordings in the resting state were obtained using Medelec Profile EEG equipment (Oxford, UK) and standardized international 10–20 nomenclature via Ag/AgCl plated-disk electrodes, as recommended by the American Electroencephalographic Society (14). A maximum resting condition of the subject for 20 min at room temperature was assured during the procedure. The reference electrode was placed at the midline. The electrode impedance was carefully kept below 5 kΩ. HV and photic stimulation were employed as the activation methods. The filtering interval, frequency and amplitude of the device were adjusted to 10–50 Hz, 30 mm/sec and 100 μV, respectively (15). All of the recordings were evaluated by the same neurologist (A. Ö.), who was unaware of the diagnoses of all of the subjects.

Psychometric assessments

The children in the enuretic and control groups were assessed using the Maudsley Obsessive Compulsive Questionnaire (MOCQ), which has four subscales (doubt, cleanness, control and slowness), for assessing obsession and compulsion (16), the Beck Child Depression Inventory (BCDI) for scoring depression (17, 18) and the State and Trait Anxiety Inventory for Children (SAI-C, TAI-C) for scoring anxiety (19). In this study, all psychometric tests used were approved by the Turkish Health Ministry in terms of their validity and reliability. In addition to these assessments, the Diagnostic and statistical manual of mental disorders, 4th revised edn. (DSM-IV) was used for diagnosis in all children and their parents in all of the groups (20).

Statistical analysis

All the data are given as mean ± standard deviation. An independent sample *t*-test, a χ^2 test and Pearson correlation analysis were used for statistical analysis. A two-tailed *p*-value of <0.05 was accepted as statistically significant.

RESULTS

Sociodemographic data for the groups are summarized in Table I. Twenty-eight children (68.2%) in the enuretic group had a positive family history of nocturnal enuresis among first-degree family members, but only three (15.7%) in the control group ($p < 0.01$). Compared to controls, 24 (58%) children had birth complications and 16 (39%) were born prematurely in the enuretic group ($p < 0.001$). The time at which real words were first spoken occurred significantly later in the enuretic children ($p < 0.01$).

The frequency of EEG abnormalities was significantly higher in the children with enuresis and their dry siblings than in the control group ($p < 0.01$). In the enuretic group, 20 children (48.7%) had a variety of special patterns in the resting EEG recordings (Table II). Of these children, only one (2.4%) had epileptiform EEG patterns. The only focal epileptiform abnormality observed was centrotemporal spike discharges. The

Table I. *Demographic characteristics and differences in physical development of children with primary monosymptomatic nocturnal enuresis and controls*

Characteristic	Enuretic group ($n = 41$)	Control group ($n = 19$)
Gender		
Female	17 (41.4%)	8 (42%)
Male	24 (58.5%)	11 (58%)
Average age (years)	11.53 ± 2.93	11.37 ± 1.35
Average age of the mother (years)	35.6 ± 7.6	34.5 ± 2.3
Average age of the father (years)	41.0 ± 5.7	39.6 ± 4.0
Positive family history	28 (68.2%)*	3 (15.7%)
Birth complication	24 (58%)**	0
Born prematurely	16 (39%)*	0
Time to walk (months)	13.9 ± 4.6	13.2 ± 4.6
Time to speak first word (months)	22.2 ± 7.4*	17.5 ± 4.4
Time to gain bowel control (months)	23.8 ± 8.0	21.7 ± 8.5

* $p < 0.01$, ** $p < 0.001$ compared with controls.

most commonly seen EEG pattern in the enuretics was increased theta activity in the posterior region. In addition, an HV response was evaluated as a non-specific sign of brain dysfunction or cortical instability as a result of delayed maturation. Figure 1 shows an example of an increased HV response in a child with primary monosymptomatic nocturnal enuresis. The resting EEG recordings revealed an increased HV response in 16 children (39.2%) in the enuretic group, nine (31%) in the sibling group and two (10.5%) in the control group. The frequency of an increased HV response was statistically significantly higher in the children with enuresis and their dry siblings than in the control group ($p < 0.001$).

Concerning the parents, there were no significant differences in unemployment, marital separation, living conditions, age or education levels between the groups. Thirteen children (31.7%) in the enuretic group and two of the controls (10.5%) had psychiatric problems ($p > 0.05$). Of the enuretics, two had depression, two had obsessive–compulsive disorder (OCD), two had attention deficit hyperactivity disorder (ADHD), one had conduct disorder, one had motor tic disorder, one had temper tantrums, two had separation anxiety and two had school phobia. One child had selective mutism and one had motor tic disorder in the control group. There were two psychiatric problems (6.8%) in the sibling group: one had chronic motor tic disorder and one had conversion. Five mothers (12.1%) and three fathers (7.3%) in the enuretic group had psychiatric problems such as OCD, depression, conversion or chronic motor tic disorder. In the control group, the corresponding rates were 10.5% and 3.4%. There was no statistically significant difference in the frequency of parental psychiatric problems between the enuretic and control groups ($p > 0.05$). Scores for obsession and compulsion, depression and anxiety did not differ significantly between the groups, but the TAI-C scores of the children with enuresis were higher than those of the controls (Table III) ($p < 0.01$). There was no correlation between the scores on any of the scales and either the age of the children, being an eldest child, psychiatric problems of the parents, living in broken or single-parent homes or EEG abnormalities.

DISCUSSION

Nocturnal enuresis is a very common behavioral disturbance in children and, without doubt, its etiology is multifactorial. It has been demonstrated that there is an increased incidence of signs of developmental delay in enuretic children (9, 10). Similarly, we found that the time at which real words were first spoken occurred significantly later in the children with primary monosymptomatic nocturnal enuresis. As reported by other

Table II. *Frequency of EEG abnormalities*

EEG abnormality	Enuretic group ($n = 41$)	Dry siblings ($n = 29$)	Control group ($n = 19$)
Non-epileptiform abnormalities (total)	19 (46.3%)*	8 (27.5%)*	3 (15.7%)
Low voltage records	8	2	0
Posterior alpha	4	1	1
Dysrhythmia	3	4	2
Paroximal activity	4	1	0
Epileptiform abnormalities (total)	1 (2.4%)	0	0
Increased HV response	16 (39.2%)**	9 (31%)**	2 (10.5%)

* $p < 0.01$, ** $p < 0.001$ compared with controls.

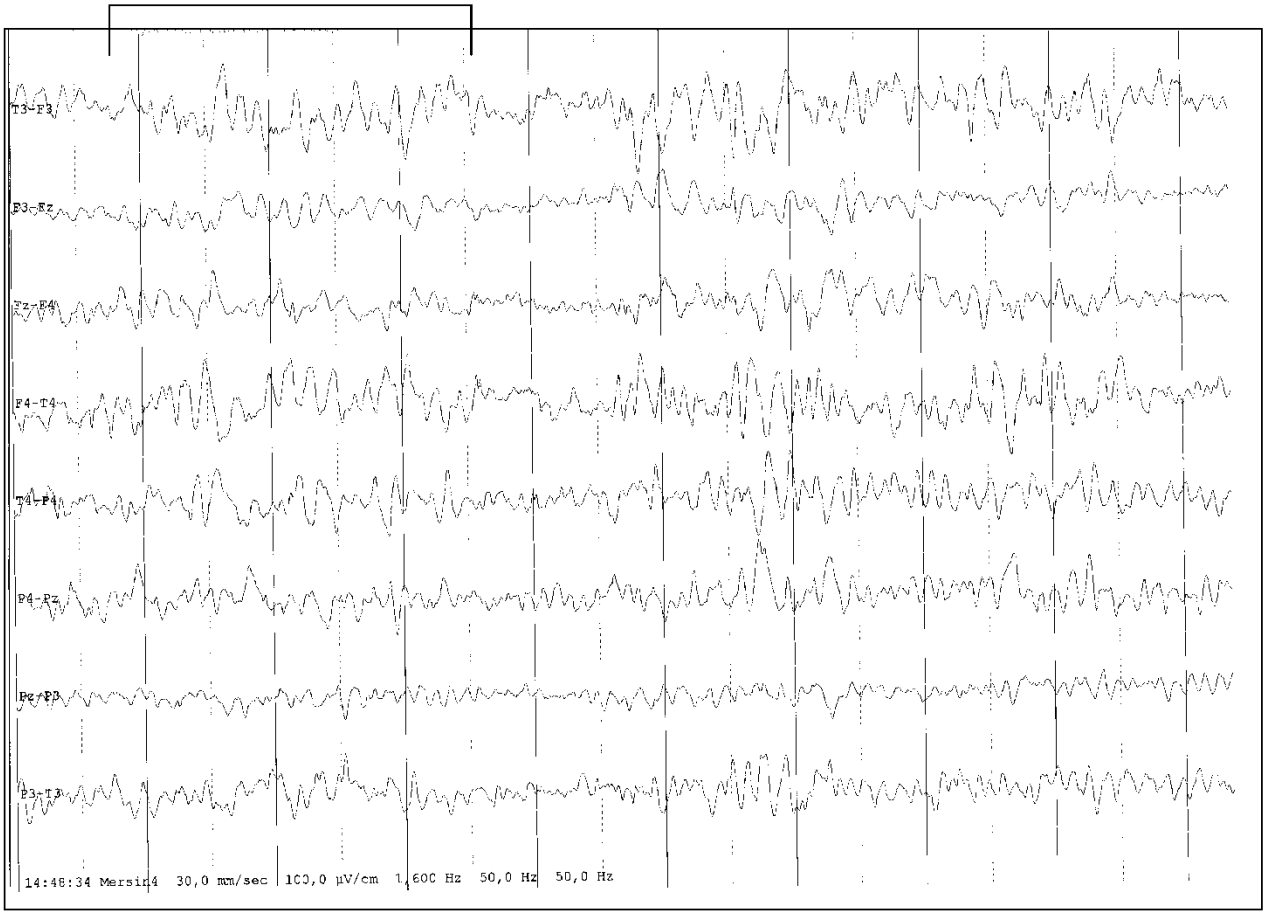

Fig. 1. An example of an increased HV response in a child with primary monosymptomatic nocturnal enuresis.

investigators, our results suggest that a developmental delay in speech might be one of the factors connected to enuresis. On the other hand, most of the children with enuresis in the present study had birth complications and 39% of them were born prematurely. This finding may account for the difference in speaking time between enuretics and controls. These results are in accordance with those reported by Jarvelin (9) and we suggest that children who experienced birth trauma and who have possible neurological damage have a risk of becoming enuretic. In addition, a familial influence was seen in the present study, with 68.2% of children with primary monosymptomatic nocturnal enuresis having a positive family history of nocturnal enuresis among first-degree family members. An increased incidence of enuresis in children with a positive familial history has been documented and slow maturation of the nervous system controlling bladder function may be of genetic origin (21).

Table III. *Results of psychometric assessments (scale scores) in the children with primary monosymptomatic nocturnal enuresis and controls*

Scale	Enuretic group ($n = 41$)	Control group ($n = 19$)
BCDI	11.8 ± 4.5	11.1 ± 4.3
TAI-C	37.1 ± 4.5*	32.5 ± 8.6
SAI-C	33.0 ± 4.9	33.6 ± 4.3
MOCQ (total)	16.2 ± 4.7	16.1 ± 2.8
Doubt subscale	5.3 ± 1.9	4.4 ± 2.2
Cleanness subscale	4.2 ± 1.5	4.2 ± 1.7
Control subscale	3.7 ± 1.7	3.9 ± 1.1
Slowness subscale	2.8 ± 1.4	3.0 ± 1.3

* $p < 0.01$ compared with controls.

Although the mechanisms are poorly understood, it is believed that a developmental delay in CNS control may be a cause of nocturnal enuresis. More recently, attention has focused on the delayed functional maturation of the central nervous system (8); however, there is certainly evidence of immature and non-specific EEG patterns in children who persistently wet the bed (12, 22, 23). In the present study, EEG also demonstrated a slightly higher rate of non-specific changes in the children with primary monosympto-

matic nocturnal enuresis and their dry siblings. These findings are consistent with those of previous reports. We demonstrated that an HV response in the electroencephalogram was more common in children with primary monosymptomatic nocturnal enuresis than in the controls. The HV phenomenon consists of shorter or larger runs of regular, sinuous, slow waves of high amplitude and with a frequency of 2.5 to 3.5 sec, which are usually maximal over the posterior head regions, in response to forced breathing. In the literature, an HV response was evaluated as a non-specific sign of brain dysfunction or cortical instability as a result of delayed maturation and a limited number of studies were designed to clarify the relationship between nocturnal enuresis and selective cortical dysmaturity (11, 12). Similar to those previous reports, we found an increased HV response in the children with primary monosymptomatic nocturnal enuresis and our results indicate that insufficient cerebral maturation is one of the important factors in the pathogenesis of enuresis. In contrast to the previous studies, we determined the HV response in dry siblings of enuretic children. We showed that the frequency of an increased HV response was significantly higher in the dry siblings than in the control group. To our knowledge, this is the first demonstration that dry siblings of enuretic children have an increased HV response. These interesting findings may emphasize the relationship between insufficient cerebral maturation and the genetic origin of nocturnal enuresis.

It can be expected that the prevalence of psychiatric problems will be higher in enuretics or vice versa. Although the relationship between nocturnal enuresis and behavioral problems is controversial, this phenomenon often leads to significant psychosocial problems for children and their parents (6, 7). However, children with nocturnal enuresis have more psychiatric problems, such as a greater feeling of exclusion from society, reduced self-esteem, anxiety disorder, depression, temper tantrums, nail-biting, fire-setting, conduct problems and ADHD (5, 21, 24). We evaluated scores for obsession and compulsion, depression and anxiety, but found no difference between the groups. Only trait anxiety scores were higher in the children with primary monosymptomatic nocturnal enuresis. On the other hand, the frequency of psychiatric problems was found to be higher in the enuresis group, although it did not different significantly from that in the control group. In addition, we did not find any difference in the frequency of parental psychiatric problems between enuretics and non-enuretic children. All of these results possibly suggest that stress factors may represent a much greater risk of psychiatric problems in children with enuresis. Moreover, the higher trait anxiety scores of the enuretic children may indicate that they were generally under more stress than the non-enuretic children. There are several possible explanations for the higher anxiety level of children with enuresis. Firstly, children with nocturnal enuresis can experience perplexity, humiliation, social isolation, a fear of detection by others and a sense of immaturity (25). Secondly, these children are frequently aware of the social and emotional consequences of their condition and therefore feel unable to sleep at a friend's house or sense that they are different from their friends. Also, they are inevitably exposed to a greater risk of social humiliation by siblings, relatives and perhaps increasingly intolerant parents (7).

According to the multifactorial model, increased frequencies of a high-level HV response in resting-state EEG recordings and anxiety suggest that delayed cortical maturity and comorbid psychiatric disorders might be important factors in the pathogenesis of nocturnal enuresis. The HV responses of the dry siblings of the enuretic children found in this study may emphasize the relationship between insufficient cerebral maturation and the genetic origin of nocturnal enuresis. Longitudinal studies are needed in order to evaluate the follow-up of the mental development and psychiatric disorders of the children with nocturnal enuresis.

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