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Nocturnal Enuresis Antecedent Is Common in Adolescents with Migraine

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Key Words
Nocturnal enuresis · Migraine · Headache · Hypothalamus

Abstract
Background: Migraine and nocturnal enuresis are highly prevalent disorders with striking similarities. Both have unknown pathophysiology and are considered multifactorial, with neurobiological, genetic, and behavioral aspects involved. Interestingly, the same neurological structures thought to be involved in the pathogenesis of migraine are also thought to be involved in nocturnal enuresis. Few studies, however, have addressed these conditions as related. The aim of this study was to evaluate the antecedent of nocturnal enuresis in a large consecutive series of adolescents with migraine as compared to controls. ***Methods:*** A total of 151 subjects were evaluated; 50 had episodic migraine, 50 had chronic migraine, and 51 were control subjects. All patients were submitted to a detailed questionnaire addressing epidemiological and clinical aspects. ***Results:*** There was a strong correlation between the clinical history of nocturnal enuresis and the diagnosis of migraine. ***Conclusion:*** Our study showed that nocturnal enuresis is a precursor of migraine and a migraine comorbid condition. These results support a pathophysiological linkage between the two conditions.

Introduction

Migraine is the most common neurological complaint in adolescents [1], leading to high levels of school absences [2] and being associated with several comorbid conditions, such as sleep disorders, anxiety, and depression [3].

The term 'comorbidity' refers to the non-casual association between two or more morbid conditions in one person [4]. For migraine, the study of comorbidities is potentially important for many reasons: (1) the presence of comorbidities has a significant impact on the correct diagnosis of migraine due to symptomatological concurrency; (2) their occurrence may either impose therapeutic restrictions or create new treatment opportunities; (3) they may increase the impact of migraine and the search for medical resources to treat them, and (4) the study of comorbidities may shed light on the physiopathological mechanisms underlying migraine [4].

Disorders that share the same pathophysiological features or have similar associated conditions are possibly comorbid. Interestingly, nocturnal enuresis shares striking similarities with migraine. Both conditions are highly prevalent [5] and have a pathogenesis that is currently unknown. These conditions are considered multifactorial, with neurobiological, genetic, and behavioral aspects

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Box 1. Diagnostic criteria for enuresis according to the ICD-10 Classification of Mental and Behavioral Disorders by the World Health Organization

A	Child aged at least 5 years, with a mental age of at least 4 years
B	Involuntary voiding of urine that occurs at a frequency of at least twice a month in children aged <7 years, and at least once per month in children aged ≥7 years
C	Enuresis not a consequence of epileptic attacks or of neurological incontinence, and not a direct consequence of structural abnormalities of the urinary tract or any other nonpsychiatric medical condition
D	No other psychiatric disorder that meets the criteria for other ICD-10 categories
E	Duration of at least 3 months

all being involved [6], and the same pathophysiological structures are thought to be involved in both conditions [7]. Finally, both conditions are associated with high incidences of sleep disorders, anxiety, and depression [6, 8].

The aim of this study was to evaluate the antecedent of nocturnal enuresis in adolescents with migraine, linking nocturnal enuresis to migraine as either a precursor or a comorbid condition.

Subjects and Methods

The study was performed between August 2008 and August 2009; all patients were recruited in schools, pediatric or neuropediatric facilities. We enrolled patients with migraine and control subjects of both sexes, aged 10–20 years, who had parents able to understand the consent form and explanations given by the research team and who agreed to participate in the study.

Control subjects did not suffer from migraine or any other primary headache syndrome and were selected among adolescents with the same sociodemographic background as the experimental subjects. The exclusion criteria were chronic diseases, unstable medical condition, secondary headaches, continuous usage of any kind of medication, drug addiction, or abusive alcohol use. All of the subjects' parents provided written consent for the study, which was approved by the local ethics committee.

Migraine was defined according to the International Classification of Headache Disorders diagnostic criteria, Second Edition (ICHD-2) [9], and chronic migraine (CM) was defined according to the 2006 appendix criteria [10]. All patients were submitted to a detailed headache questionnaire that was divided into sections about demographic data (probing age, gender, ethnic background, and educational level for both the patient and their parents), clinical data (age of headache onset, duration, frequency, pain intensity, and the presence of aura), history of nocturnal enuresis, and age of urinary control.

The diagnosis of nocturnal enuresis was defined according to the ICD-10 Classification of Mental and Behavioral Disorders by the World Health Organization (Box 1) [11].

Data Analysis

The χ^2 test (without Yates correction) was used for categorical data comparisons. The mean values between the two patient groups were compared using the independent Student t test (t); ANOVA (one-way analysis of variance) (F) was used when there were three samples. When the ANOVA showed significant differences, Bonferroni multiple comparisons test was performed to verify the significance of our results.

Multiple logistic regression analysis was performed to verify the relationship between nocturnal enuresis (as the independent variable) and migraine (as the dependent variable). The dependent variables were analyzed in pairs: control group (CG) × episodic migraine (EM), CG × CM, and EM × CM. The results are shown as odds ratio (OR). Mean ± SD are reported unless stated otherwise. A p value of <0.05 was considered to indicate statistical significance; all tests were two-tailed. Ninety-five percent confidence intervals (CI) were calculated for the difference between means and OR. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 11.5.1 for Windows.

Results

A total of 187 subjects were referred to the study. From this total, 36 subjects were excluded: 8 refused to take part in the study, 6 did not give reliable history information, and 22 had at least one exclusion criteria. The analysis of the remaining 151 subjects is shown below. Among them, 50 had EM, 50 had CM, and 51 were enrolled as the CG.

There were significant differences between the three groups regarding age ($F(2,148) = 9.7$, $p < 0.001$), controls being older (15.4 ± 1.9 years) than subjects with EM (14.1 ± 2.8 years) and CM (13.4 ± 2.7 years). The proportion of women was higher in the CM group (CG = 29%, EM = 29% vs. CM = 42%, $\chi^2(2) = 10.9$, $p = 0.004$).

Clinical Characteristics of Migraine

The headache age of onset for EM patients was 8.6 ± 2.9 years, and attack duration had a median of 4.5 h. For the CM group, age of onset was 7.8 ± 2.3 years with a median duration of 6.0 h. There were no significant differences regarding age of onset ($t(98) = –1.5$, 95% CI = –0.23 to 1.87, $p = 0.125$) or the duration of headache episodes ($t(98) = –0.4$, 95% CI = –3.94 to 2.62, $p = 0.689$). The presence of aura was significantly higher in the CM group compared to the EM group (48 vs. 28%, $\chi^2(1) = 4.24$, p = 0,039).

The mean score of pain intensity in patients with CM was significantly higher than the scores in the EM group (7.3 ± 1.4 vs. 6.1 ± 1.9, $t(98) = 3.5$, 95% CI = 0.52–1.88, $p = 0.001$).

Table 1. Average age for urinary control achievement and the presence of antecedent nocturnal enuresis

Comparison between groups	Average differences	95% CI (difference)	p
Age of control, years			
CG × EM	−1.81	−3.36 to −0.25	0.017
CG × CM	−2.67	−4.22 to −1.11	<0.001*
EM × CM	−0.86	−2.42 to −0.70	0.554
Antecedent of enuresis			
CG × EM		$\chi^2(1) = 17.89$	<0.001*
CG × CM		$\chi^2(1) = 26.50$	<0.001*
EM × CM		$\chi^2(1) = 1.05$	0.305

* $p < 0.017$ is considered to indicate statistical significance according to Bonferroni correction.

Table 2. Analysis of the clinical characteristic of pain in patients with and without the antecedent of nocturnal enuresis

Characteristics of pain	t(98)	95% CI (difference)	p
Age of migraine onset, years	0.20	−0.98 to 1.20	0.843
Duration, h	−1.67	−6.11 to 0.52	0.098
Frequency, days/month	−1.32	−6.15 to 1.25	0.191
Intensity of pain	−2.18	−1.51 to −0.07	0.032*

* Significant.

Age of Urinary Control Achievement

In the CG, the mean age of nocturnal urinary control achievement was 3.3 ± 3.0 years, which was significantly lower than in the EM group (5.1 ± 3.4 years) and the CM group (6.0 ± 3.3 years; $F(2,148) = 9.0$, $p < 0.001$). However, the age of urinary control achievement in the two migraine groups was statistically similar ($p = 0.554$).

Diagnosis of Nocturnal Enuresis and Migraine

Patients with migraine had significantly more often a history of nocturnal enuresis than the CG (CG = 12%, EM = 41% vs. CM = 49%, $\chi^2(2) = 28.9$, $p < 0.001$).

Multiple logistic regression analysis was performed to verify if the relationship between nocturnal enuresis (as the independent variable) and migraine (as the dependent variable) were independent of age and sex. The dependent variables were analyzed in pairs (CG × EM, CG × CM, and EM × CM; table 1).

Student t test analysis was performed to verify the clinical characteristics of pain in patients with or without the antecedent of nocturnal enuresis. There were no differences regarding the age of migraine onset or the duration or frequency of the attacks. There was, however, a significant difference in the reported intensity of pain (table 2).

When considering only the patients with CG and EM, the chance of patients with nocturnal enuresis experiencing EM was 18.7 times higher than in patients without enuresis. Furthermore, when considering the CG and the patients with CM, the chance of patients with enuresis presenting CM was 22.8 times the chance of patients without enuresis.

Discussion

The same neurological structures are possibly involved in migraine and nocturnal enuresis. In 1933, Henriksen [12] first suggested the important role of the hypothalamus in migraine by treating 42 migraine patients with an extract of the posterior lobe of the pituitary containing vasopressin and oxytocin.

The hypothalamus is also important in the control of nociception. Animal studies performed by Carstens [13] with electrical stimulation of the hypothalamus showed a reduction of pain in experimental animals that led to analgesia, which is presumed to be caused by the several opioid peptides expressed in the hypothalamus. In fact, several peptides associated with the hypothalamus, such as angiotensin II, vasopressin, calcitonin, and somatostatin, have antinociceptive effects [14].

After puberty, females suffer from migraine 3 times more often than men, which is another main argument for the hypothesis that the onset of migraine could be caused by hypothalamic networks [14]. One third of the affected women have their first migraine attack at menarche, and the relative risk of having a migraine attack is higher in the perimenstrual period, implying that hypothalamic networks related to luteinizing hormone-releasing hormone (LNHR) secretion are involved [15]. Finally, the hypothalamic role in maintaining homeostasis, in the regulation of the circadian rhythm, and in coordinating the sympathetic and parasympathetic nervous system implies that the hypothalamus is a main structure in the pathophysiology of migraine [14].

The premonitory symptoms that occur prior to migraine attacks have been recognized for centuries and include vague symptoms of hunger, thirst, lassitude, tiredness, yawning, and a desire to micturate, all of which may

reflect hypothalamic dysfunction that precedes a migraine attack [14].

The role of the hypothalamus in migraine has been widely used to explain several migraine comorbidities. Hypothalamic neural circuits have been used to associate migraine, mood, and anxiety disorders [16]; a hypothalamic dysfunction in appetite regulation and energy homeostasis associates migraine and obesity [17], and the hypothalamic role in regulating the circadian rhythm explains the increased prevalence of migraine in patients with sleep disorders [18, 19].

The hypothalamus plays an important role in the beginning of micturition. Early animal studies, such as those performed by Gjone in 1966 [20], showed that electrical stimulation of forebrain structures, such as the hypothalamus, the anterior cingulate gyrus and septal nuclei, can elicit bladder contractions. Interestingly, although most of these regions send fibers to the brainstem, only the hypothalamic area projects specifically to the pontine micturition center, which is responsible for decreases in urethral pressure, relaxation of the pelvic floor, increases in the intravesical pressure, and normal micturition [21]. Modern neuroimaging studies using positron emission tomography (PET) scans show that the hypothalamus is activated during micturition [22].

Finally, neurometabolic studies have shown that altered levels of melatonin, an important metabolite for the regulation or arginine-vasopressin levels as well as for the regulation of the circadian rhythm, may affect nocturnal micturition continence [23]. Very recent studies have established that altered levels of melatonin are found in patients with CM [24], as well as in patients with several migraine comorbidities [25].

Those facts constitute an important rationale for the findings of our study. The fact that the subjects in the CG were significantly older than the patients in the migraine groups lowered the chances that young patients who would possibly develop migraine later were erroneously enrolled in the CG.

Our study also had a predominance of female subjects in all the three groups (controls, EM, and CM), with a significantly higher proportion of female subjects in the CM group.

The female predominance among patients with migraine was expected. A recent population-based epidemiological study assessing children and adolescents by Kröner-Herwig et al. [26] revealed that females are more commonly affected with all types of headaches, and that this predominance increased toward the onset of adolescence. Another study by Bigal et al. [1] which studied only adolescent subjects regarding the diagnosis of migraine also revealed a higher incidence of diagnosis in females. However, it was interesting to find in our study that, even in a predominantly female cohort, the incidence of nocturnal enuresis antecedence was higher, although nocturnal enuresis is considered a predominantly male disorder. Large epidemiological studies performed by Butler et al. [27], Verhulst et al. [28], and Watanabe et al. [29] all revealed that males are more often diagnosed with nocturnal enuresis. None of these studies, however, controlled the subjects for comorbid disorders.

In our study, the fact that the antecedent of nocturnal enuresis was more common among patients with EM and CM, even with a female predominance among the groups, reinforces a possible pathophysiological linkage between the two conditions. Recently, according to Park et al. [30], the existence of a shared pathophysiological substrate between migraine and primary nocturnal enuresis may explain their coexistence.

In earlier observations, vasopressin regulating renal water excretion and peripheral blood flow was consistently raised only in the patients who experienced vomiting during an attack of spontaneous migraine [31]. In contrast, Poole and Lightman [32] reported six cases with a history of increased urinary frequency during migraine, and marked diuresis and natriuresis were associated with a significant fall in urinary arginine vasopressin.

In conclusion, Park et al. [30] state that although evaluations of vasopressin secretion have been reported with conflicting results in migraine, inhibition of vasopressin secretion and increased urinary frequency during a spontaneous attack of migraine are the most common findings and symptoms. These convincingly suggest that migraine might be associated with altered hypothalamic activity [30].

Our study also found that, among patients with the antecedent of nocturnal enuresis and the diagnosis of migraine, no differences regarding the age of migraine onset or the frequency or duration of migraine attacks were found. However, it was very interesting to find that the patients with the antecedent of nocturnal enuresis reported higher pain intensity.

Animal studies performed by Dafny et al. [33] showed that the hypothalamus is one important site in pain modulation. The hypothalamus also plays a similar role in humans [34]. Nociceptive stimulation activates neurons in the trigeminal nucleus caudalis. These neurons project to multiple brainstem, thalamic, hypothalamic, and telencephalic sites that distribute sensory information to multiple cortical regions in sequence. These pathways,

such as the trigeminohypothalamic tract as well as several others, play a major role in the modulation and in the experience of pain [34].

The age of onset, frequency, and duration of pain in migraine, however, are multifactorial. The age of onset is largely influenced by environmental and genetic determinants [35]. The same can be said about frequency and duration of pain. These two aspects of migraine are largely influenced by either non-modifiable factors, such as gender, race, socioeconomic status, and genetic background, or modifiable factors, such as symptomatic medication use or overuse, caffeine abuse, obesity, psychiatric factors, and stressful life events [36].

This study has a potential limitation. The collection of enuresis data by retrospective maternal report may result in a selective recall bias. However, the fact that subjects as a group and normal control subjects had similar rates of enuresis mitigates this possibility.

Our study demonstrates a significant relationship between nocturnal enuresis and migraine. Nocturnal enuresis antecedent being consistently higher among adolescents with migraines and a significantly higher age of urinary control achievement suggest a putative role of the hypothalamus in the pathophysiology of migraine.

Recently, Carotenuto et al. [37] proposed that nocturnal enuresis and migraine could be linked by a cortical system arousal dysfunction with primary nocturnal enuresis being considered as migraine equivalent. This idea was supported by the studies of Dexter [38] and Bruni et al. [19] that confirm the existence of a strong association between migraine and sleep disorders such as pavor nocturnus, somnambulism, and enuresis.

In conclusion, further studies are necessary to elucidate the relationship between migraine and nocturnal enuresis, which, to date, is considered multifactorial. These data may have implications for the classification of migraine into pathophysiological categories, whether structural, environmental, or genetic, with further implications for the diagnosis and treatment of migraine.

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