A Possible Pathogenic Linkage Among Headache, Migraine, and Nocturnal Enuresis in Children

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Purpose: This study aims to evaluate the prevalence of headaches and migraine in children with nocturnal enuresis (NE) and to improve knowledge on these conditions. In particular, for this purpose, a possible pathogenic relationship linking both conditions and the impact of headaches and migraine on NE persistence was evaluated.

Methods: Researchers enrolled 123 children with NE, aged between 5 and 15 years, referred to the Service of Pediatrics, Campus Bio-Medico University Hospital of Rome between January 2014 and January 2015. Parents of all children enrolled in the study were invited to complete a self-reported questionnaire. The study protocol was approved by the Human Research Ethics Committee of Campus-Bio-Medico University. The NE group data was compared with the data of a control group (107 children).

Results: Of the eligible patients, 7.8% suffer from headaches/migraine (mean age, 9.63 years; interquartile range [IQR], 3.5 years) and 47.1% have a family history of headaches (mean age, 8.46 years; IQR, 3.75 years). Of the 8 patients with headaches, all are male, 3 have tension-type headaches (2 of them have maternal family history) and 5 have migraine (3 of them have maternal family history). Of the 35.3% with a migraine family history (mean age, 8.36 years; IQR, 3.5 years), 22 are male, and 14 are female. Three of these patients have migraine. A total of 92.2% suffer from NE but not from headaches (mean age, 8.43 years; IQR, 3 years). Of these patients, 33 are female (35.1%), and 61 are male (64.9%). In the control group, 4.7% (5 out of 107) of the children suffer from headaches, and of these, 4 are affected by nonmigraine headaches and 1 by migraine.

Conclusions: In conclusion, according to the hypothesis, NE and headaches/migraine could be linked by several similarities.

Keywords: Melatonin; Enuresis; Child

INTRODUCTION

Headache is a common complaint among children that occurs in 75% of adolescents and 25% of young children; it is also the most common neurological disease observed in clinical practice [1,2]. The International Headache Society classification system is distinguished into primary and secondary headache disorders [3]. In particular, migraine without aura and tension-type head-
ache (TTH), both primary disorders, are the 2 most common types of headaches in children and adolescents. A migraine is a primary headache and has an important socioeconomic impact on children's and parents' quality of life and relationships [4]. The mean prevalence of (nonmigraine) headaches is 54.4% (95% confidence interval [CI], 43.1–65.8) and the mean prevalence of migraine is 9.1% (95% CI, 7.1–11.1) [5]. The World Health Organization recognized these disorders as a major public health concern, in particular by ranking migraine at 7th place among all worldwide diseases causing ictal disability [6]. For these reasons, the clinical approach to an infant with headache should be systematic and seek early recognition and management [7].

Migraine can be defined as paroxysmal disorder with a natural fluctuation between a low and high frequency pattern. Its etiology is complex and includes modifiable and nonmodifiable risk factors. It is a chronic, painful syndrome with aspects such as psychiatric comorbidity, decreased quality of life, and environmental factors that can all influence the success of its treatment. A high and increasing attack frequency can lead to ‘chronic migraine’ (CM), which then becomes resistant to acute as well as prophylactic migraine medications. CM is defined as having more than 15 headache days in a month, with at least half of these showing migraine features for a period of at least 3 months [8]. Considering TTH in children and adolescents, there is a wide range of prevalence [9]. Many children and adolescents exhibit an overlapping pattern of migraine and TTH [10]; moreover, by the end of the teenage years, the diagnosis of TTH may convert to migraine or vice versa [11].

Nocturnal enuresis (NE) is the most common developmental pediatric disorder. It can be defined as wetting while asleep after the age of 5 years. The estimated prevalence of NE is age-related and highly variable because diagnostic criteria are heterogeneous [12]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), NE is defined as repeated voiding of urine into bed or clothes while asleep in children older than 5 years.

NE occurs when there is poor arousal from sleep in response to a sensation of full bladder in association with an overactive bladder and an excess of nocturnal urine production. Other risk factors that are shown to be associated with NE include: delay in attaining bladder control, physiological factors such as constipation, fecal incontinence, daytime urinary incontinence (UI), caffeine consumption, sleep apnea, upper airway obstructive symptoms, lower socioeconomic status, and black race [13].

NE can be distinguished into 2 subgroups: primary and secondary NE. A child with primary NE has never been continuously continent for more than 6 months; secondary NE relates to relapse after at least 6 months of dryness. Secondary NE is also associated with organic or psychological causes such as urine infection, sexual abuse, diabetes, obstructive sleep hypoventilation, neurogenic bladder, or externalizing disorders such as attention-deficit/hyperactivity disorder or conduct disorder.

NE, without daytime symptoms of bladder dysfunction, is called monosymptomatic NE (MNE), while NE with any daytime lower urinary tract symptoms is considered a non-MNE [14].

The aim of this study is to evaluate the prevalence of headache in children with NE and to increase knowledge on these 2 conditions. In particular, for this purpose, this study evaluated a possible pathogenic relation linking both conditions and the impact of headache on NE persistence.

MATERIALS AND METHODS

The present study is an observational study conducted on 123 children with NE, aged between 5 and 15 years, referred to the Service of Pediatrics, Campus Bio-Medico University Hospital of Rome between January 2014 and January 2015. The study protocol was approved by the Human Research Ethics Committee of Campus-Bio-Medico University (approval number: 07.16.TS). The community comparison group consisted of 107 children of the general population whose data were collected from family pediatricians in the Rome area.

Children and their families were asked to participate in the study at the end of the clinical evaluation and after obtaining informed consent. Parents were queried regarding their child's birth, past medical and family history, current medical conditions, and medications. The inclusion criterion was primary NE while exclusion criteria included secondary NE, urogenital malformations, renal failure, and diabetes. Parents of all children enrolled in the study were invited to complete a self-report questionnaire adapted from the CHILD/Adolescent Hardship questionnaire [15]. The information gathered through the 13-item questionnaire included 4 items regarding general data: name, surname, gender, age; 9 items concerning headaches: presence/absence of headaches in child, presence/absence of headaches among relatives, age of headache onset, daily/nightly symptoms, duration of each attack, pain characteristics (location, type, degree, associated symptoms), drugs used during the attack, relation with physical and daily activities, and relation with certain types of food.
RESULTS

The study population included 123 children with NE. Of these, 15 patients were excluded (11 for secondary NE, 3 for diabetes, 1 for urogenital malformations), and 6 patients refused to participate. Therefore, the study consisted of 102 children; 69 male (68%) and 33 female (32%), aged between 5 and 15 years (mean age, 8.52 years; interquartile range [IQR], 3 years). In particular, the male mean age was 1.75 years higher than the female mean age. The age in the comparison group was between 5 and 14 years (mean age, 8.19 years); 61% were male and 39% were female.

Of the 102 eligible patients, 8 (7.8%) suffer from headaches (mean age, 9.63 years; IQR, 3.5 years) and 48 (47.1%) have a family history of headaches (mean age, 8.46 years; IQR, 3.75 years). Of the 8 patients with headaches, all are male, 3 have TTH (2 of them have maternal family history) and 5 have migraine (3 of them have maternal family history) (Fig. 1, Table 1).

Considering family history, 33 patients (32.4%) (12 female and 21 male patients) have a maternal family history of headaches (mean age, 8.21 years; IQR, 2.5 years), 19 children (18.6%) (6 female and 13 male patients) have a paternal family history of headaches (mean age, 9.11 years; IQR, 4 years), and 6 patients (5.9%) (2 female and 4 male patients) have grandparents suffering from headaches (mean age, 7.33 years; IQR, 3 years).

Of the 12 patients (11.8%) with a family history of TTH (mean age, 8.75 years; IQR, 4.5 years), 8 are male and 4 are female patients. Two of these patients have TTH.

Of the 36 patients (35.3%) with a family history of migraine (mean age, 8.36 years; IQR, 3.5 years), 22 are male and 14 are female patients. Three of these patients have migraine.

Ninety-four patients (92.2%) suffer from NE but not from headaches (mean age, 8.43 years; IQR, 3 years). Of these patients, 33 are female (35.1%) and 61 are male patients (64.9%).

In the control group, 5 out of 107 children (4.7%) suffer from headaches; of these, 4 are affected by nonmigraine headaches and 1 by migraine.

DISCUSSION

Migraine shares striking similarities with NE. Both conditions are two common multifactorial pediatric disorders involving genetic, behavioral, and neurologic aspects with a complex pathophysiology which is still not completely known [16].

Studies have reported that children with primary NE and migraine might show dysfunction of the autonomic nervous system [17]. In particular, several studies observed sympathetic and parasympathetic nervous system hyperactivity in both enuretic and migraine children; moreover, Yerdel et al. [18] demonstrated that the most common dysfunction in migraine is sympathetic hypofunction.

Considering anatomical aspects, neurological structures are thought to be involved in the pathogenesis of migraine and NE. Montagna [19] showed that the periaqueductal grey matter, the dorsal raphe nuclei and the locus coeruleus represent the “migraine generator”; furthermore, the locus coeruleus plays an important role in the activation of arousal circuits and it is also related to NE pathophysiology.

Some authors have confirmed the well-known relationship between sleep disorders and migraines: somnambulism, sleep terrors, and enuresis were observed in children affected by headaches [20,21]. This is probably based on common pathophysiological substrates [22]. In particular, the increased prevalence of migraine in patients with sleep disorders is associated with the hypothalamus regulation of circadian rhythm [23].

Clinical literature has demonstrated contrasting results regarding the onset of migraine or enuretic attacks during the night; in particular, micturition tends to occur during non–rapid-eye-movement sleep, while migraine attacks seem to be
Headache and Enuresis in Children

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In particular, Butler et al. [33] observed that males are more often diagnosed with NE. Despite this observation, our study found that there is a significant correlation between maternal headache and NE in children. In particular, of a total of 36 patients with a family history of migraine, 23 mothers have cephalalgic symptoms (23 of 36 [64%]; odds ratio, 5.78).

Furthermore, comparing the results of the NE group with the data of the control group, it was observed that the prevalence of headache in the NE group (7.8%) is higher than the prevalence of headache in the control group. Specifically, in the NE group, the number of children with migraine (5 out of 8 of those children with headache) is higher than the number of children with migraine (1 out of 5 of those children with headache) in the control group.

Finally, migraine and NE also share psychological factors: they are both associated with high incidences of internalizing problems such as anxiety and depression that negatively impact quality of life [34,35].

In conclusion, according to our hypothesis, NE and headaches/migraine could be linked by several similarities. Further studies are necessary to elucidate the relationship between headaches and NE and between family history of headache and NE. In particular, additional studies might address the issue of analyzing headache prevalence considering a bigger sample size and a long follow-up period evaluation. It could also be interesting to assess the impact of NE treatment on cephalalgic symptoms. Moreover, validated scales should be used to diagnose headaches in young children and also to distinguish migraine and nonmigraine headaches in order to highlight all of the specific features.

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