Impact of Puberty in Pediatric Migraine: A Pilot Prospective Study

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Background and Purpose The short-term evolution of pediatric migraine remains unclear. We aimed to describe the evolution of migraine before and after puberty and its relationship with lifestyle habits.

Methods We prospectively selected prepuberal patients from a neuropediatric unit who had a migraine diagnosis. Their medical history, migraine characteristics and impact, and lifestyle habits were recorded at the baseline visit. After 2 years we performed a telephone follow-up assessment.

Results Nineteen patients were recruited (age 10.2 ± 2.9 years, mean ± SD; 57.9% female), of whom 27.5% had migraine with aura. The accompanying symptoms had changed at the follow-up, with significantly higher prevalence rates of dizziness (44.4% vs. 88.9%), vertigo (11.1% vs. 66.7%), mood changes (38.9% vs 83.3%), confusion (5.6% vs. 77.8%), and allodynia (27.8% vs. 61.1%). Sleep disturbances (5.6% vs. 38.9%) and schedule changes (0% vs. 38.9%) increased significantly as triggers. Prodromal symptoms became more prevalent (16.7% vs. 50%), with a higher proportion of sleep disturbances reported (50.0% vs. 87.5%).

Conclusions Prodromal symptoms increase in pediatric migraine after 2 years, and some trigger factors for migraine become more prevalent, including sleep disturbances. New accompanying symptoms are also identified. These changes provide information about how migraine changes during puberty along with physical and lifestyle changes, and represent a dynamic physiopathological process that deserves more research.

Key Words migraine, puberty, adolescence, natural history; lifestyle.

INTRODUCTION

The estimated prevalence of migraine in children and adolescents has ranged from 3% to 10%. The prevalence of migraine increases with age, and it is well described that the prevalence is similar in males and females before puberty, switching to a female preponderance from adolescence. Several studies of long-term outcomes have shown that the annual remission rate of childhood migraine is around 6% within the first 3 years, but decreases to 1–2% over a long-term follow-up (10 to 50 years).

Headache represents an important cause of disability in children, being one of the five most-important causes of illness-related school absenteeism. A study found that children with migraine lose a mean of 7.8 school days a year due to all illnesses, of which 2.8 were a direct consequence of their migraine, compared with a mean of 3.7 lost days in children without migraine. Pediatric migraine is associated with specific comorbidities such as asthma, allergy, sleep disorders, and a higher prevalence of psychopathological symptoms, which might transfer into adulthood.

Most population-based studies of pediatric migraine have retrospective designs, include...
broad age groups of children and different headache types, and involve clinical data that were mainly obtained using self-administered questionnaires rather than by physician evaluations. Only a few prospective studies have investigated the evolution of headache during the transition from childhood to adulthood. These studies have been particularly focused on describing prognostic factors and diagnostic changes, with only a few analyses of the symptomatic evolution over time as a secondary objective. Moreover, few studies have described the relationships between migraine and sleeping or eating habits, with very little or no information being available on the relationship between pediatric migraine and lifestyle habits.

The aim of the present study was to describe the evolution of pediatric migraine during the years around puberty, as well as its relationships with eating and lifestyle habits.

**METHODS**

We conducted an observational, prospective study of patients from a specialized neuropaediatric unit that met the International Classification Headache Disorders III beta criteria for migraine (with or without aura) from January to December 2015. The study was approved by the local ethics committee [Vall d’Hebron Research Institute (VHIR) Clinical Research Ethics Committee, PR (AMI)15/2013]. The legal representatives of all patients read and signed the informed consent for the study, including for the patient’s assent in all cases. All patients were developmentally staged according to the Tanner Scale, and only patients in a Tanner I stage (prepuberal) were included. The presence of other primary headache diagnoses and/or puberty signs in a physical examination were exclusion criteria.

At the baseline visit (BL), all patients were assessed by a trained neuropaediatrician, recording demographic data, medical, personal, and familial histories, the time to the neurology visit, and the findings of a physical examination. Birth information was also recorded, and preterm births were defined as those that occurred before 37 complete weeks of gestation. The migraine characteristics recorded included age at migraine onset, attack frequency and duration, number of attacks before this first evaluation, pain characteristics, description of the aura symptoms, triggers, functional impact [as measured on the Pediatric Migraine Disability Assessment Score Scale], and the history of received treatments. A specific anamnesis was performed in order to describe both prodromal and accompanying symptoms, which included confusion (defined as the inability for clear and coherent thought) and vertigo (defined as the subjective sensation of the movement of objects). Both patients and their parents (when necessary) were interrogated in order to obtain the most-accurate information. Lifestyle and eating habits, physical activity (measured as the proportion of time spent performing physical exercise and sedentary activities), sleeping routine, school performance, possible discrimination situations, and anxiety items were queried. Sleep habits were measured using the BEARS (B, bedtime issues; E, excessive daytime sleepiness; A, night awakenings; R, regularity and duration of sleep; S, snoring) sleep screening tool, and anxiety traits and state were measured using the Spanish adaptation of the State-Trait Anxiety Inventory for Children scale.

All patients were re-evaluated by a neurologist in a telephone 2-year follow-up visit (FUP). All of the migraine characteristics were newly recorded at this visit, and the patients completed a self-administered on-line questionnaire querying their lifestyle and eating habits, sleeping habits, anxiety, and puberal physical changes.

Descriptive and frequency statistical analyses were performed, and comparisons were made using the SPSS statistical package (version 23.0 for Windows, IBM Corp., Armonk, NY USA). The statistical significance of intergroup differences was assessed using Pearson’s chi-square or Fisher’s exact test for dichotomous and categorical variables, the linear-trend chi-square test for ordinal variables, and Student’s t-test or the Mann-Whitney U test for quantitative variables. The paired t-test and the Wilcoxon signed-rank test were used to assess pre-post changes in numerical variables at 2 years after the BL. A probability value of p<0.05 was considered statistically significant for differences between the two study visits: BL and FUP.

**RESULTS**

This study recruited 19 patients with an age at inclusion of 10.2±2.9 years (mean±SD), which included 11 (57.9%) females. The diagnoses at inclusion were migraine without aura in 13 (72.2%) and migraine with aura in 5 (27.8%), while 73.7% had family history of headache, most commonly affecting the patient’s mother (42.1%). The most-frequent conditions in their past medical histories were infant colic (26.3%), recurrent abdominal pain (21.1%), preterm birth (15.8%), and asthma (15.8%). The findings of physical examinations were normal in all patients except for one who presented with generalized and symmetric hyperreflexia and another who presented with prognathism. Nine patients (47.4%) had previously undergone neuroimaging, which had produced no significant findings. The age at migraine onset was 8.2±3.6 years, the average time before a neurology visit was longer than 12 months in 57.9% of the patients, and 78.9% had experienced more than 10 migraine attacks (Table 1).

Regarding pain characteristics, patients described their
pain more frequently as compressive (61.1%) or throbbing (50.0%), and bilateral (55.6%). The most frequently reported migraine triggers at the BL were stress or anxiety (50.0%) and weather changes (50.0%). Only three patients (16.7%) reported prodromal symptoms, the most frequent of which was noise sensitivity (11.1%).

Follow-up was completed by 95% (n=18) of the 19 patients. After 2 years, all patients had experienced puberal physical changes.

We identified one patient whose migraine diagnosis switched from migraine without aura to migraine with aura. All patients with aura (27.8%) had visual aura. There was no significant change in the location or quality of head pain, nor in the attack frequency or duration (Table 2). However, at the FUP there was a significant change in some of the pain-accompanying symptoms, with higher reported prevalence rates of dizziness (88.9% and 44.4% at BL and FUP, respectively), vertigo (66.7% and 11.1%), mood changes (83.3% and 38.9%), confusion (77.8% and 5.6%), and allodynia (61.1% and 27.8%) (p<0.05) (Fig. 1).

There were significant increases in the prevalence of migraine triggers in patients who reported sleep disturbance

| Table 2. Changes in migraine characteristics from the BL to the FUP |
|------------------|------------------|
|                  | BL       | FUP      |
| Age, years       | 10.2±2.9 | 12.3±2.7 |
| Diagnosis        |          |          |
| Migraine without aura | 14 (77.8) | 13 (72.2) |
| Migraine with aura  | 4 (22.2)  | 5 (27.8)  |
| Aura             |          |          |
| Visual           | 5 (27.8)  | 5 (27.8)  |
| Sensory          | 2 (11.1)  | 0 (0)    |
| Pain quality     |          |          |
| Throbbing        | 9 (50.0)  | 9 (50.0)  |
| Compressive      | 11 (61.1) | 10 (55.6) |
| Explosive        | 2 (11.1)  | 4 (22.2)  |
| Implosive        | 1 (5.6)   | 0 (0)    |
| Others           | 2 (11.1)  | 2 (11.1)  |
| Pain location    |          |          |
| Unilateral       | 8 (44.4)  | 6 (33.3)  |
| Bilateral        | 10 (55.6) | 12 (66.7) |
| Attack duration  |          |          |
| <4 hours         | 0 (0.0)   | 4 (22.2)  |
| 4–24 hours       | 13 (72.2) | 9 (50.0)  |
| 25–48 hours      | 2 (11.1)  | 4 (22.2)  |
| 49–72 hours      | 2 (11.1)  | 1 (5.6)   |
| >72 hours        | 1 (5.6)   | 0 (0.0)   |
| Monthly attack frequency | |          |
| <3 attacks       | 10 (55.6) | 9 (50.0)  |
| 3–6 attacks      | 5 (27.8)  | 7 (38.9)  |
| 6–10 attacks     | 1 (5.6)   | 2 (11.1)  |
| >10 attacks      | 1 (5.6)   | 0 (0.0)   |
| Symptomatic medication use and response | |          |
| NSAIDs           | 18 (100.0) | 15 (83.3) |
| NSAIDs improvement | 15 (83.3) | 15 (83.3) |
| Simple analgesics | 6 (33.3)  | 12 (66.7) |
| Simple analgesics improvement | 4 (22.3)  | 10 (55.5) |
| Triptans         | 0 (0.0)   | 2 (11.1)  |
| Triptans improvement | 0 (0.0)  | 2 (11.1)  |
| Preventive treatment |        |          |
| Ongoing          | 4 (22.3)  | 2 (11.1)  |
| Past             | 3 (16.7)  | 5 (27.8)  |
| PedMIDAS disability |        |          |
| Little or none   | 7 (38.9)  | 5 (27.8)  |
| Mild             | 7 (38.9)  | 9 (50.0)  |
| Moderate         | 2 (11.1)  | 3 (16.7)  |
| Severe           | 2 (11.1)  | 1 (5.6)   |

Data are mean±SD or n (%) values. No significant changes were found in these characteristics.

BL: baseline visit, FUP: follow-up visit, NSAIDs: nonsteroidal anti-inflammatory drugs, PedMIDAS: Pediatric Migraine Disability Assessment Score.
(38.9% and 5.6% at FUP and BL, respectively) and schedule changes (38.9% and 0%) \( p<0.05 \) (Fig. 2). One female patient who had previously experienced an isolated premature menarche had identified this as a migraine trigger in the BL. Six female patients had experienced menarche at the FUP, with menses identified as a migraine trigger in five (83.0%) of them.

Prodromal symptoms were more prevalent at the FUP (50.0%) than at the BL (16.7%, \( p<0.05 \)), with a tendency of presenting with nausea that did not differ significantly between these two time points (22.2% vs. 0%, respectively; \( p=0.052 \)) (Figs. 3 and 4).

Eight patients completed all the items in the on-line questionnaire regarding lifestyle and eating habits. We observed significant differences only in fruit intake, with a lower proportion of patients eating fruit daily at the FUP (42.9%) than at the BL (84.6%, \( p<0.05 \)). A higher proportion of patients reported disturbances in sleep-time regularity and sleep duration at the FUP (87.5%) than at the BL (50.0%, \( p<0.05 \)). No significant differences were observed in other characteristics such as eating habits, physical activity, school performance, possible discrimination situations, sleeping habits, or anxiety items in the self-completed on-line questionnaire.

A subgroup analysis was performed to compare patients with and without aura. Differences in physical exercise and sleep duration were observed between the two groups, with
patients who had aura performing less regular exercise (12.5% vs. 68.4%, \( p < 0.05 \)) or not performing any exercise (37.5% vs. 10.5%, \( p < 0.05 \)). Moreover, the sleeping time was shorter in patients with aura (7.9±1.4 hours) than in those without aura (9.2±1.1 hours, \( p < 0.05 \)).

**DISCUSSION**

We have performed a prospective 2-year follow-up study of prepuberal children with a migraine diagnosis with the aim of better describing the evolution of pediatric migraine during puberty.

**Change in migraine diagnoses during the peripuberty transition years**

Previous studies have produced inconsistent results for changes in migraine diagnoses during the peripuberty transition years. The broad school-based epidemiological study performed by Ozge et al.\(^{20}\) found a high rate (approximately 70%) of diagnostic changes. A Finnish prospective study of preschool children that included different types of recurrent headache found that the diagnosis changed in 32% of the children from migraine to tension-type headache.\(^{21}\) Although those studies included larger numbers of patients, the included patients also spanned wide age ranges and different headache diagnoses. In contrast to previous studies, we analyzed a small series of very strictly selected patients who were diagnosed in detail and followed by headache specialists in a specialized unit.

Remission did not occur in any of the patients in our sample. It is known from previous longitudinal studies that 20–30% of children with migraine experience remission at follow-up.\(^{5,11}\) However, the follow-up was longer in those studies, and the reported remission rates mostly related to adult ages. Our study applied a different approach, focusing on the changes in migraine during puberty. Since we exclusively selected prepuberal patients and followed them for a shorter period of time, it is not surprising that no patient had experienced remission at follow-up. This would give an idea of how migraine is a dynamic process that changes during puberty, but perhaps remission might not occur until more-advanced maturative stages.

**Migraine triggers**

During puberty, the main characteristics and the location of pain remain roughly the same, whereas triggers change and prodromal symptoms start to appear. In particular, sleep disturbances and irregular schedule changes are newly identified as triggers by children, and nausea tends to become a more-frequent prodromal symptom. Sleep deprivation has been widely reported as one of the main migraine triggers that appear over time,\(^{11}\) which the present study has confirmed. A previous cross-sectional study of subjects older than 16 years identified some new triggers such as hormone impact, alcohol, smoking, and neck pain.\(^{22}\) These results are consistent with our results showing that new triggers can appear together with changes in habits during puberty and adolescence.

**Identification of accompanying symptoms**

After puberty, children tend to be more likely to identify certain accompanying symptoms. Our study found that confusion, allodynia, mood changes, vertigo, and dizziness were more frequent at the FUP. The previous Finnish study found that osmophobia, dizziness, and balance disturbances became more common during the follow-up, whereas restlessness, flushing, and abdominal symptoms became less frequent. Nevertheless, Kelman\(^{22}\) found that photophobia, phonophobia, and dizziness declined with age. Also, motion sickness had been described as an accompanying symptom whose frequency increases over time.\(^{11}\) These disparities must be treated cautiously due to the heterogeneity of the studies and considering that many of them included both migraine and tension-type headache. It is possible that changes in the pathophysiological mechanisms of migraine during adolescence explain these new symptoms. Nevertheless, we cannot ignore that children might be more capable of describing certain specific conditions over their development, which might introduce bias into the findings.

**Modifications in sleep and exercise habits**

This study also shows that during the transition from prepuberty to adolescence, children present modifications in sleep and exercise habits that may influence the evolution of their migraine. During adolescence, the presence of headache has been associated in different studies with irregular sleeping and eating habits, low physical activity, smoking, and caffeine intake.\(^{23}\) However, these results must be interpreted cautiously, since sleep disturbance might be more difficult to identify during childhood and some children may find it difficult to associate experiences of headaches with such problems.

It was particularly interesting that the patients with aura tended to perform less exercise and have a shorter daily sleep duration. These findings are of special interest due to its possible relationship with migraine pathophysiology, and give us a valuable clue for identifying other factors (aside from pharmacological treatment) that might interfere in the course of this disease over time.

This study performed a prospective follow-up with careful patient selection and specialized neuropediatric evaluations.
for the migraine diagnosis and migraine features, as well as other comorbidities and puberal development stage. It brings a specially interesting insight into a subject that has never been directly assessed in previous studies—the changes in migraine during the puberal transition. Moreover, the prospective follow-up of the cohort was performed by a neurologist, and the survey of lifestyle and eating habits was completed by the patients themselves responding to the identical standardized questions asked at the BL. This a very accurate and homogeneous sample, which allowed us to accurately evaluate the evolution of this pathology.

The main limitation of this study was the small size of the sample, which made it difficult to obtain definite and comparable results, as well as a medium-term follow-up of 2 years that cannot represent the complete transition to adulthood. It is quite probable that a longer follow-up and especially a larger sample would identify other prodromal symptoms as described in previous studies, such as the influence of hormones or alcohol. Also, the telephone-based design of the FUP was a limitation to evaluating certain clinical aspects such as the body mass index or Tanner stage. On the other hand, it must be considered that younger children might have difficulties in identifying or expressing certain neurological symptoms. This might interfere with the prevalence rates and changes in migraine characteristics and their relationships with lifestyle habits, particularly with sleep disturbances. Nevertheless, the present findings have identified factors that will be interesting to keep investigating so that we can better understand the changes that migraine suffers during life, especially in the teenage years when change is exponential.

Many changes occur in migraine characteristics from prepuberty to puberty and adolescence, along with changes in the pattern of triggers, migraine characteristics, and prodromal and accompanying symptoms. A significant proportion of patients also show variations in sleeping and exercise habits, which might be associated with the changes observed in migraine features. Migraine is a disease that affects people throughout their lives and deserves medical follow-up strategies that consider both its physical and lifestyle aspects.

Author Contributions
Conceptualization: Alfonso Macaya, Patricia Pozo-Rosich. Data curation: Elena Fonseca, Víctor José Gallardo. Formal analysis: Elena Fonseca, Víctor José Gallardo. Investigation: Elena Fonseca, Marta Torres-Ferrús, Alfonso Macaya, Patricia Pozo-Rosich. Methodology: Marta Torres-Ferrús, Víctor José Gallardo, Alfonso Macaya, Patricia Pozo-Rosich. Software: Víctor José Gallardo. Validation: Víctor José Gallardo, Patricia Pozo-Rosich. Writing—original draft: Elena Fonseca. Writing—review & editing: all authors.

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Conflicts of Interest
MTF reports personal fees and non-financial support from Allergan, Novartis and Chiene outside the submitted work.
PP-R has received honoraria as a consultant and speaker for: Allergan, Almirall, Chiesi, Eli Lilly, Novartis and Teva. Her research group has received research grants from Allergan and has received funding for clinical trials from Alder, Electrocore, Eli Lilly, Janssen Cilag, Novartis. And Teva. PP-R does not own stocks from any pharmaceutical company. All of this, is outside the submitted work.
EE, AM, VJG declare no conflicts of interest.

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