



Original Article

Premonitory Symptoms in Episodic and Chronic Migraine From a Pediatric Headache Clinic

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ABSTRACT

Objective: We evaluated the frequency of six commonly reported adult migraine premonitory symptoms in children and adolescents with episodic and chronic migraine and elicited psychological or behavioral comorbidities that may be associated with these symptoms.

Background: Premonitory symptoms are commonly reported in the adult migraine population; however, little information is available for the pediatric population.

Methods: Data were collected on new patients being evaluated in our multidisciplinary pediatric headache clinic over a six-month time interval. The data collected from patients diagnosed with migraine were then reviewed for the following premonitory symptoms: yawning, neck stiffness, fatigue, increased urination, mood changes, and food cravings. History was obtained regarding the frequency of headaches and other associated behavioral or psychological problems.

Results: A total of 176 patients were enrolled over a six-month interval, ranging in age from four to 18 years (mean age 12 years); 64% were female, and 42% (74 of 176) of the subjects had at least one premonitory symptom. Patients with migraine with aura were noted to have a significantly higher association with premonitory symptoms (59%, 30 of 51) ($P < 0.05$). Anxiety disorder was also significantly associated with premonitory symptoms (55%, 11 of 20) ($P < 0.05$). Fatigue and mood changes were the most commonly reported premonitory symptoms.

Conclusions: Premonitory symptoms occurred frequently in our population of pediatric patients with migraine. Fatigue and mood changes were the most frequent symptoms. There were no significant differences in premonitory symptoms by gender or age group (less than 12 years versus greater than 12 years). Anxiety and migraine with aura were correlated with an increased likelihood of premonitory symptoms.

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Introduction

Migraine is a common neurological condition in the pediatric population. Prevalence rates of about 10% are generally seen in school-aged children with increasing prevalence in the adolescent population.¹ Migraine attacks can frequently cause absences from

school, and family stressors can become magnified when caring for an ill child. Compared with children with *tension-type* headaches, children with migraine often have more severe, disabling headaches.² In addition, about 25% patients with migraine have an aura preceding their headaches manifested by transient symptoms, often a visual or sensory disturbance, which may also contribute to the overall disability of these headaches.³

In the adult migraine population, premonitory symptoms (PSs) have been self-reported by most patients before their migraine headaches. These generally precede the migraine by two to 48 hours.⁴ These symptoms may be varied in their presentation, both subjective and objective, and can include fatigue, mood changes, and excessive yawning. In two different series of adult patients, the presence of at least one PS ranged from 30% to 80% before the onset of their headaches.^{5,6}

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PSs in pediatric patients with migraine are less well characterized. Previous studies have been small and retrospective, but PSs were frequently present. Karsan et al, in a retrospective study of 100 patients with predominantly chronic migraine, primarily noted fatigue, mood change, and neck stiffness.⁷ There were no differences related to age, sex, or headache diagnosis. In another retrospective study evaluating 103 patients, 67% reported at least one PS.⁸ The most frequently reported symptoms were face changes, fatigue, and irritability. The presence of PSs and the specific symptom reported did not vary with age or migraine subtype.

Patients and methods

We surveyed new patients with migraine (both episodic and chronic) who were aged four to 18 years, presenting to our multidisciplinary pediatric headache clinic. Patients and families were questioned regarding the presence of PSs in the 48 hours before their migraine headaches. Six PSs were chosen that were most frequently reported in selected adult studies.^{4,5} These included yawning, neck stiffness, fatigue, food cravings, increased urination, and mood changes. We limited the symptoms in number to use only those commonly seen in the adult population to increase the reproducibility of symptom report. Although face changes were commonly noted in the Cuvellier et al. pediatric migraine study, it was not generally mentioned in adult patients and thus was excluded from our study.⁸ Patients and parents or guardians were questioned regarding these symptoms occurring before their headaches. The headache diagnoses were assigned according to the International Classification of Headache Disorders-3.⁹ Patients were enrolled over a six-month time interval.

To minimize the effects of prophylactic medication on the reported symptoms, patients enrolled in the study were not taking any prescription preventive migraine medication. Other epidemiologic factors obtained were history of aura and comorbid psychological or behavioral disorders such as anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD). Diagnoses of these psychological comorbidities was based on parent or guardian report of medical history. No objective clinical or disability measures were utilized. Medication overuse headache as an additional diagnosis was also elicited. Approval for the study was obtained from our institution's investigational review board.

Statistical analysis

Reported patient characteristics were summarized as frequencies and percentages. The prevalence of PSs was assessed in three ways: prevalence of any symptom among all patients, prevalence of specific symptoms among all patients, and prevalence of specific symptoms among patients with at least one symptom. Prevalence of any symptom, prevalence of fatigue, and prevalence of mood changes was compared by patient characteristics using chi-square or Fisher's exact tests and odds ratios with 95% confidence intervals. As patients could have more than one type of migraine and more than one symptom, each migraine type and each symptom was assessed individually. Multivariable logistic regression was used to determine independent risk factors for PSs. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). *P* value < 0.05 was deemed significant. Sample size was based on the available data.

Results

From June through December 2016, 176 subjects were enrolled ranging in age from four to 18 years. Sixty four percent enrollees

(112 of 176) were girls, and the mean age of all patients was 12 years. Of the 176 patients, 51 were diagnosed with migraine with aura, and 54 of 176 (30%) had chronic migraine. Most of the subjects (122 of 176, 70%) were aged ≥ 12 years. In the under 12 group, males accounted for 60% of the subjects. From age 12 to 18 years, females predominated (74%).

As part of the initial history, the subjects (or their family members) were asked questions about comorbid conditions, ongoing medication use, and family history. The most common comorbid conditions were psychiatric issues (anxiety, depression, self-harm, behavior issues) (18%), obesity (14%), and ADHD (9%). Medication overuse headache, as defined by taking a headache-specific abortive two or more times per week or nonspecific pain medication three or more days per week for three months according to the International Classification of Headache Disorders-3 criteria, was noted in 35% of the patients with chronic migraine.

A history of PSs was elicited in 42% of the subjects with migraine (74 of 176). Subjects who had migraine with aura had statistically significant greater occurrence of PS than other migraine groups; a negative correlation was noted in the group without aura (Table 1).

Chronic migraine sufferers also had more complaints of PS than those with episodic migraine without aura. Age, gender, medication overuse, and obesity were not significant predictors of PS. Subjects with a psychiatric disorder were more likely to have PS than those without a psychiatric disorder (59% versus 39%, odds ratio [OR] = 2.25). Anxiety was significantly associated with PS; this association was not present with depression or attention deficit disorder (ADD)/ADHD (OR = 4.67) (Table 1).

TABLE 1.
Prevalence and Odds of Any Premonitory Symptom by Patient Characteristics

| Gender | N (%) | Odds Ratio | <i>P</i> Value |
|--------------------|---------|--------------------|----------------|
| Male | 24 (38) | | |
| Female | 52 (46) | 1.39 (0.74, 2.60) | 0.309 |
| Age | | | |
| <12 | 22 (42) | | |
| ≥ 12 | 54 (44) | 1.05 (0.55, 2.02) | 0.8795 |
| Chronic migraine | | | |
| No | 48 (39) | | |
| Yes | 28 (52) | 1.66 (0.87, 3.17) | 0.1224 |
| Migraine with aura | | | |
| No | 46 (37) | | |
| Yes | 30 (59) | 2.45 (1.26, 4.77) | 0.0075 |
| Migraine no aura | | | |
| No | 49 (54) | | |
| Yes | 27 (31) | 0.38 (0.21, 0.71) | 0.002 |
| Medication overuse | | | |
| No | 57 (41) | | |
| Yes | 19 (51) | 1.52 (0.73, 3.14) | 0.2589 |
| Obesity | | | |
| No | 62 (42) | | |
| Yes | 14 (50) | 1.39 (0.62, 3.12) | 0.427 |
| Any psychiatric | | | |
| No | 52 (39) | | |
| Yes | 24 (59) | 2.25 (1.11, 4.59) | 0.0234 |
| ADD/ADHD | | | |
| No | 66 (41) | | |
| Yes | 10 (67) | 2.88 (0.94, 8.81) | 0.0549 |
| Anxiety | | | |
| No | 61 (39) | | |
| Yes | 39 (75) | 4.67 (1.62, 13.51) | 0.0023 |
| Depression | | | |
| No | 67 (42) | | |
| Yes | 9 (50) | 1.36 (0.51, 3.61) | 0.5377 |
| Self-harm | | | |
| No | 72 (43) | | |
| Yes | 4 (40) | 0.87 (0.24, 3.20) | >0.9999 |

Abbreviations:

ADD = Attention deficit disorder

ADHD = Attention-deficit/hyperactivity disorder

TABLE 2.
Adjusted Odds of Premonitory Symptoms and Comorbid Factors in Migraine

| Premonitory Symptoms and Co-morbid Factors | OR | Lower CI | Upper CI | P Value |
|--|-------|----------|----------|---------------|
| Female | 1.29 | 0.631 | 2.637 | 0.4857 |
| Age <12 | 1.671 | 0.767 | 3.641 | 0.1963 |
| Chronic migraine | 0.884 | 0.253 | 3.087 | 0.8472 |
| Migraine with aura | 1.463 | 0.469 | 4.56 | 0.5117 |
| Migraine no aura | 0.425 | 0.106 | 1.707 | 0.2279 |
| Medication overuse | 1.246 | 0.556 | 2.789 | 0.5933 |
| Obesity | 1.319 | 0.558 | 3.116 | 0.5284 |
| Any psychiatric | 2.196 | 1.031 | 4.676 | 0.0415 |
| ADD/ADHD | 2.791 | 0.875 | 8.904 | 0.083 |
| Anxiety | 6.28 | 1.745 | 22.599 | 0.0049 |
| Depression | 0.593 | 0.129 | 2.719 | 0.5016 |
| Self-harm | 0.67 | 0.119 | 3.765 | 0.6491 |

Abbreviations:

ADD = Attention deficit disorder

ADHD = Attention-deficit/hyperactivity disorder

CI = Confidence interval

OR = Odds ratio

Any psychological diagnoses and anxiety were significantly associated with odds of experiencing a premonitory symptom are indicated in bold.

In multivariable assessment, the presence of any psychiatric disorder was the only significant independent risk factor for PS. The odds of PS were 2.2 times greater among patients with a psychiatric diagnosis compared with those without a psychiatric diagnosis. Of psychiatric illnesses, anxiety was the only diagnosis with a significant association with the presence of PS, although the presence of ADD/ADHD was nearly significantly associated with PS (Table 2).

Fatigue was the predominant PS in all groups (68% of all PS) followed by mood changes (57%). Neck stiffness was described by 8% of the subjects with PS, while yawning (1%), food cravings (3%), and urinary changes (0%) were all insignificant. Fatigue as a premonitory sign was greater among patients with anxiety (50%) compared with those without anxiety (29%) (OR = 2.63). Mood change as a PS was greater among patients with migraine with aura (37%) compared with those with migraine without aura (20%) (OR = 2.38). An association between anxiety and an increased prevalence of mood change failed to reach significance ($P = 0.09$).

Discussion

Our study revealed that PS was frequent, with nearly half of our subjects experiencing these symptoms before their migraine. Fatigue and mood changes were the most commonly reported symptoms. Previous pediatric studies reported higher percentages of PSs, and this may be attributed to the fact that our study limited the symptoms to the six most commonly reported ones in adult studies.^{7,8} PS also had a mild but not significant association with increasing frequency of migraine attacks with a majority of patients with chronic migraine reporting PS.

Aura symptomatology was significantly associated with PS in our study. Fifty-nine percent of patients with migraine with aura had PS. In adult studies, a majority of patients with migraine with aura also acknowledged PS, with 79% and 81% noted in prior studies. Variable results were noted with relationship to aura and attack frequency in adult reports.^{5,6} One pediatric chart review study did not report an increase in PS with aura,⁷ and another large study did not categorize aura symptomatology in their chart review study of 100 patients.⁸

PS occurred slightly more often in individuals with more frequent migraine attacks, but the increase failed to reach significance. Patients with medication overuse also had greater prevalence of PS, although the numbers were small and the association was not significant.

A relationship with cortical spreading depression has not been thought to play a role in the onset of PS; many PS manifestations are probably related to dopamine involvement because yawning, dysphoria, and fatigue can be related to central hypersensitivity to dopaminergic activation.¹⁰ Serotonergic pathways probably also may play a major role. Patients with migraine with aura may be more observant to changes in physiology with relationship to onset of their discrete aura with their migraine attacks.¹¹

Consistent with prior studies, we noted PSs to be more common in females than in males (46% versus 38%).^{7,8} Females, both as adults and as children, may be more sensitive to pain related to stimuli, hence this increased sensitivity may translate to greater vigilance regarding symptoms associated with their migraine attacks.¹² Possibly this increased sensitivity translates into a greater observation for other changes such as those seen in PS.

Patients with psychiatric comorbidities were more likely to have PS (59%), and although the numbers were relatively small, this was most significant in patients with comorbid anxiety (75%). Individuals suffering from anxiety disorders are known to be hypersensitive to changes that might lead to increased cues regarding discomfort and pain or possibly may be related on a biochemical basis to serotonergic or dopaminergic pathways, with increased introspection to physiological changes.¹³ ADD with or without hyperactivity was noted to have an increased association with PS that almost reached significance. Children and adolescents with ADD/ADHD may have some anxiety symptomatology associated with their behavioral disorder, which may play a role in this finding.¹⁴ Psychological or behavioral disorders and concomitant PS have not been well studied in the adult or pediatric population, and further evaluation of this relationship would be helpful.

Migraine attacks cause major disruptions in the lives of the pediatric patient with migraine and his or her family.¹⁵ We educate our patients that prompt treatment with a triptan or other appropriate rescue medication is vital to limiting the impact of the attack. In the subset of patients who exhibit PSs, these symptoms can be the advanced warning that a patient or family needs to be prepared for immediate treatment at the onset of symptoms.

As we have shown, patients with migraine with aura and those with chronic migraine are more likely to note PS as are those individuals with comorbid medication overuse, obesity, or psychiatric problems, particularly ADHD or anxiety. In our study population, fatigue and mood changes were overwhelmingly the most reported PSs. Our results strongly suggest that we should be discussing PSs with our patients and families, educating them to observe and report PSs, even including this information in their headache journals or diaries. This is particularly a consideration in the higher-risk subgroups noted above, such as those with aura and anxiety disorders, as they may use this information to be ready to initiate prompt rescue treatment of migraine attacks.

Studies of larger cohorts are needed to better characterize PSs in the pediatric population.¹⁶ Information regarding PS was elicited retrospectively in our clinic patients. Therefore reporting was subject to recall bias effects and may mitigate the extent of reporting especially in those patients with infrequent migraine headaches.

Migraine attacks cause major disruptions in the lives of the pediatric patient with migraine and his or her family. Educating patients that prompt treatment with a triptan or other appropriate rescue medication is paramount to limiting the impact of the attack. In the subset of patients who exhibit PSs, these can be used to possibly mitigate migraine attacks with behavioral modifications, such as the practice of biofeedback or relaxation therapy techniques, or ensuring that negative lifestyle effects are minimized, such as ensuring adequate hydration or assessing

impact of sleep deprivation or missing meals. These symptoms can serve as a reminder to parents or guardians that a migraine attack may be imminent and appropriate abortive treatments should be readily available.

Conclusion

PSs were common in our pediatric patients with migraine. Fatigue and mood changes were the most commonly reported symptoms, similar to previous studies. Anxiety and migraine with aura were significantly associated with an increased likelihood of PSs in our group of patients. Elicitation of these symptoms may improve management and lessen the effect of migraine headaches in children and adolescents.

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