Pediatric headache

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Purpose of review

Headaches occur frequently in the pediatric population and have a significant impact on both the patient and their family. Migraine, the most common headache disorder for which patients see a physician, still remains underdiagnosed and undertreated. Recent studies have revealed the increasing incidence of migraine and chronic migraine in the pediatric population.

Recent findings

Limitations of the present diagnostic criteria for migraine are presented, and the proposed modifications to these criteria may assist you with early recognition and ultimate treatment. New acute and preventive migraine treatment data demonstrating statistically significant benefit for the primary endpoints will be reviewed in detail. The clinically relevant impact of migraine on the pediatric patient documented by the use of the Pediatric Migraine Disability Assessment and the Pediatric Quality of Life Inventory will be discussed.

Summary

A comprehensive management approach blending the most current acute, preventive, and biobehavioral treatments will be reviewed. Further research, with novel study designs, in pediatric headaches is needed to help reveal additional pathophysiological mechanisms, improve diagnostic criteria, and advance optimal treatment. Prospective studies are needed to fully evaluate the efficacy of preventive management in this population and to establish whether early intervention might slow this disease progression.

Keywords

adolescent, childhood headache, headache, migraine, pediatric headache, pediatric migraine

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Introduction

Headache/migraine remains underrecognized, underdiagnosed, and undertreated in the pediatric population. This has potential long-term consequences with regard to disease progression. Pediatric headache and pediatric migraine are increasingly being recognized as a significant health problem. The underlying pathophysiology is presumably the same as adults, but the presenting symptoms in a developing brain are often different, especially in the young child. Early effective intervention may prevent progression and lifelong consequences, including the development of comorbidities. The 1-year prevalence of migraine was 6.3% among adolescents, 5% in boys and 7.7% in girls [1]. This common disorder is often accompanied by significant disability, affecting the child's life and school performance, and their relationship with family and peers. Early accurate diagnosis and comprehensive effective treatment are essential to minimize the impact on a child's quality of life and may result in the prevention of long-term disability.

Epidemiology and diagnosis

In a meta-analysis of pediatric headaches examining over 27 000 children, 37–51% of children by the age of seven did report a significant headache, whereas 57–82% of children by the age of 15 reported a significant headache [2]. Present epidemiology studies have employed the International Classification of Headache Disorders (ICHD)-II and the examination of the impact of frequency, socioeconomic factors, and predictors of outcome. Karli *et al.* [3], in a study of adolescents between the ages of 12 and 17 in Bursa, Turkey, noted that the prevalence of recurrent headaches was 52.2% with a slight female predominance and that a steady increase was from 42.2% in 12 year olds up to 60.7% in 17 year olds. The study also found a prevalence of 25.9% for tension-type headaches (TTH), whereas migraine headaches occurred in 14.5%. Akyol *et al.* [4], in a study from the Menderes region of Turkey, using a questionnaire-based survey, revealed that 79.6% of boys and 87.1% of the girls reported headaches [5]. A questionnaire involving a subset of these participants

revealed a prevalence of migraine of 7.8% in boys and 11.7% in girls [4,5].

Fendrich *et al.* [6] in a 3-month prevalence study in Germany used the ICHD-II; they reported a 2.6% prevalence of migraine if strict criteria were applied. Lowering the duration to 30 minutes increased the prevalence of migraine to 6.9%, with an additional 12.6% having probable migraine and 0.7% chronic migraine. Owing to the problem of self-reporting of headaches with population-based studies, which has the risk of missing infrequent headaches, several recent studies have begun to evaluate the prevalence [7] and incidence [8] of frequent headaches and the potential underlying risk factors.

The American Migraine Prevalence and Prevention study (AMPP), a validated headache questionnaire, was mailed to 120 000 households representative of the US population and was developed to investigate the epidemiology of migraine and the utilization of the medical treatments [9–11]. This study included 162 576 participants with a migraine prevalence of 5.6% in males and 17.1% in females. Of the 18 968 individuals that met the ICHD-II for migraine, 823 were between the age of 12 and 17. A subanalysis of AMPP restricted to adolescents found a 1-year prevalence of ICHD-II migraine of 6.3%, 5% in boys and 7.7% in girls [1,10]. For acute treatment, they found that 49.0% used over-the-counter treatment, 20.1% used prescription treatment, and 28.8% used both. For the adolescents, they were more likely to use over-the-counter agents (59.3%) than prescription medications (16.5%) or a combination of both (22.1%) [1,10]. The majority of adolescents (63.7%) never used preventive medication for migraine, with just 10.6% reporting current use [1,10]. One of the many observations in this study was the effect of the socioeconomic status and the familial pattern of migraine. If there was a family history of migraine, there was no effect on the prevalence because of the socioeconomic status. When there was not a family history, however, the odds ratio of having migraine increased with a lower socioeconomic status. Further analysis of the causative factors to this observation is needed, but it may explain some of the balance between the genetic and the environmental component of migraine [1,10].

ICHD criteria were initially developed to advance the clinical and scientific study of headache but have been criticized for a lack of sensitivity and specificity in diagnosing pediatric headaches, especially migraine. Some of the suggested modifications have been adopted in the notes to the criteria for migraine in the second edition of the (ICHD-II) [12] [Migraine without aura (ICHD-II–1.1)]. This has improved the sensitivity from the ICHD-I, yet it remains incomplete [13].

Migraine without aura ICHD-II – 1.1

(1) Description: Recurrent headache disorder manifesting in attacks lasting 4–72 h. Typical characteristics of the headache are unilateral location, pulsating quality, moderate-or-severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.
(2) Diagnostic criteria
  (a) At least five attacks fulfilling criteria B–D
  (b) Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
    Sleep is also considered part of the headache duration. (note 2)
    In children, 1–72 h is allowed. If between 1 and 2 h diary corroboration is required. (note 3)
  (c) Headache has at least two of the following characteristics
    (i) Unilateral location
      Bilateral headache is most common in children. Most common in frontal. (note 5, 6)
      Exclusive occipital location is worrisome based on meta-analysis. (note 6)
    (ii) pulsating quality
    (iii) moderate-or-severe pain intensity
    (iv) aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
  (d) During headache at least one of the following:
    (i) nausea and/or vomiting
    (ii) photophobia and phonophobia
    In young children, this can be inferred by their behavior by the parents. (note 8)
  (e) Not attributed to another disorder

The recognized problems include the short duration of pediatric migraines, the higher likelihood of a bilateral location, and the difficulty in describing the headache features and associated symptoms. These features may change and evolve over time owing to the variable expression of the migraine pathophysiology in a developing brain [14]. ICHD-II is a diagnostic tool and does not take into account these potential variables or the reduction of features secondary to effective treatment.

In a study evaluating the sensitivity of ICHD-II criteria for pediatric migraine, headache characteristics in 260 patients ages 18 years and younger diagnosed with migraine were summarized from standard intake questionnaires and physician-assigned clinical diagnoses were used as the gold standard for assessing the validity of ICHD-II criteria [13,15]. Among the 260 patients clinically diagnosed with migraine, 70.4% met ICHD-I criteria and 61.9% met ICHD-II criteria, including the 4–72 h headache duration. When a 1–72 h duration specified in the ICHD-II note was used, 71.9% met criteria. The most common reasons why patients' headaches did not meet the

standard criteria were the requirements for unilateral location, headache duration, and number of associated symptoms. When the ICHD-II criteria were modified to the proposed criteria for pediatrics migraine to include bilateral headache, headache duration of 1–72 h, nausea and/or vomiting, and two of five other associated symptoms (photophobia, phonophobia, difficulty thinking, lightheadedness, or fatigue), the sensitivity for diagnosing migraine improved to 84.4%. Given the significant heterogeneity in associated symptoms among children; increasing the list of associated symptoms further improves the sensitivity as given below in proposed criteria for pediatrics migraine without aura [13,15,16].

Proposed criteria for pediatrics migraine without aura

(1) Diagnostic criteria
   (a) At least five attacks fulfilling criteria b–d
   (b) Headache attacks lasting 1–72 h (untreated or unsuccessfully treated)
      Sleep is also considered part of the headache duration.
   (c) Headache has at least two of the following characteristics:
      (i) Bifrontal/bitemporal or unilateral location
      (ii) Pulsating/throbbing quality (may be inferred from their behavior)
      (iii) Moderate-or-severe pain intensity (0 to 10 scale or faces scale can be used) (numerical scale, faces scale)
      (iv) Aggravation by or causing avoidance of routine physical activity (may be inferred from their behavior)
   (d) During headache at least one of the following:
      (i) Nausea and/or vomiting (may be inferred from their behavior)
      (ii) Two of five symptoms (photophobia, phonophobia, difficulty thinking, lightheadedness, or fatigue) (0 to 10 scale or faces scale can be used)
   (e) Not attributed to another disorder

New tools and biomarkers need to be developed and integrated into the diagnostic process. Researchers have begun to examine additional tools for children to augment these criteria and include the use of drawings for the pediatric population [8,9,17,18]. At present, the ICHD-II is an improvement over the initial criteria and is currently the foundation for the diagnosis and scientific study of headache and migraine.

TTHs are generally considered mild recurrent headaches and many features are the opposite of migraine. Epidemiology studies have varied on the prevalence of these headaches in children because of the present criteria.

Although cluster headaches can begin at any age, the mean age of onset is approximately late twenties. Childhood and adolescent onset cluster has been reported, but these early onset cases appear to be rare. Only 18% of patients had their onset of cluster prior to age 18 and 2% began before the age of 10 [19].

Impact of migraine

Pediatric migraines can have a significant impact in both the child's life and the parent's life. The impact of a migraine can be measured by both the disability related to the loss of ability to participate in desired activities and the effect on quality of life in individuals. Several tools have been developed to evaluate the disability of migraine. In adults this can be addressed by using the MIDAS (Migraine Disability Assessment) tool [20–23]. The MIDAS was not adequate for pediatrics because of the differences in lifestyles of children, and subsequently the Pediatric Migraine Disability Assessment (PedMIDAS) was developed [5]. The scoring system is based on patient-based disability and has a higher scoring range than that of the MIDAS owing to the child's increased ability to miss out activities [24]. PedMIDAS can clinically be used to identify the impact of migraine in the individual pediatric patient and their response to treatment.

Another way to assess the impact of headache is with quality of life. The Short Form 20 has been used for assessing quality of life in adults [25]. In pediatric headache patients, one useful tool is the Pediatric Quality of Life Inventory (PedsQL) 4.0 [26]. PedsQL is a 23-question tool with separate, developmentally appropriate versions for age with parental and child response. It is able to identify a significant impact of the quality of life of pediatric headaches from the ages of 5–17 [27]. When the PedsQL was used to compare rheumatologic diseases, oncologic diseases, cardiac diseases, and migraine, it demonstrated an impact on quality of life similar in all disease states to related emotional and school development [27].

The impact of pediatric obesity and headache is currently being evaluated. Adult studies have shown a correlation between obesity and headache. The Pediatric-Adolescent Section of the American Headache Society demonstrated a trend of obesity with increased headache frequency and disability. Recently, 913 consecutive patients at seven centers were evaluated and 19.6% were found to be obese (BMI%ile $\geq$95%) and 36.5% at risk or obese (BMI%ile $\geq$85%). During the routine headache management, nutritional impact on headaches including weight control was discussed with all patients. Subsequent follow-up information was obtained from 213 patients at approximately 3 months and 174 patients at approximately 6 months from four centers. In the total population, the mean age was 11.9 ± 3.4 (M : F ratio: 0.7 : 1.0); mean

weight, 50.6 ± 21.6 kg; mean height, 150.3 ± 18.2 cm; mean BMI, 21.5 ± 5.9; and mean BMI%ile, 64.4 ± 29.7). The mean headache frequency per month was reported to be 12.7 ± 10.5, with the mean PedMIDAS score of 34.7 ± 42.8. At 3 months, 14.6% were obese and at 6 months 15.6% were obese. At 3 months, those obese or at-risk patients that reduced their BMI%ile had a significantly greater reduction in their headache frequency than those with weight gain, while also the obese patients that reduced their BMI%ile had a significantly greater improvement in their PedMIDAS than those without change or with a weight gain. These reported differences continued to increase at 6 months for those that reduced their BMI%ile. Thus an elevated BMI is significantly correlated with disability, suggesting a combined contribution to disability. The impact of obesity and headache in the pediatric population needs further study; but clearly in those at risk or obese that were able to reduce their BMI%ile, there was a greater degree of improvement in headache frequency and disability [28].

Treatment

A comprehensive treatment plan for pediatric headaches includes acute, preventive, and biobehavioral therapy. A practice parameter recently reviewed the available evidence for both acute and preventive therapies in detail as related to pediatric populations [29–32]. Recent additions to this area have included acute treatments with several triptans; preventive treatment with topiramate [33] and levetiracetam [34]; and the supplement use of coenzyme Q10 [35] and butterbur root extract [36].

Acute treatment

An acute effective treatment plan will end the episodic headache and return the child to normal functioning in 1–2 h. The ultimate goal of this treatment should be a quick response with return to normal activity and without relapse. In the pediatric population, the nonspecific medications including NSAIDs (ibuprofen, naproxen and sodium) and general pain relievers (acetaminophen) are frequently used. Two studies have evaluated the efficacy of ibuprofen in children. Hämäläinen reported a comparative, double-blinded, placebo-controlled crossover study of placebo vs. ibuprofen vs. acetaminophen [37] that indicated that ibuprofen was superior to both placebo and acetaminophen at both the 1 h and the 2 h time point. Lewis *et al.* [38] performed a similar study on a group of younger children using a dose of ibuprofen at 7.5 mg/kg vs. placebo with ibuprofen, again having a similar benefit. The proper use of ibuprofen and other NSAIDs needs to include early treatment, effective doses (7.5–10.0 mg/kg), and overuse avoidance (limited to 1–2 headaches treated per week).

If this initial strategy of using over-the-counter medications is ineffective or not completely effective, migraine specific therapy is oftentimes required. Children often report that the NSAIDs will work for the majority of their headaches but that they occasionally will have a moderate-to-severe migraine, where the response is either incomplete or ineffective. Triptans, migraine-specific medications, may be added to the treatment plan when needed. There are currently seven triptans approved for use in the United States for migraine in adults. Currently, in the United States, there are no approved triptans for use in the pediatric population with migraine. In Europe, nasal sumatriptan has been approved for the use of migraine in adolescents. Double-blinded, placebo-controlled studies have been performed in adolescents using almotriptan, eletriptan, rizatriptan, sumatriptan, and zolmitriptan. The majority of these studies demonstrated that the triptans were effective and well tolerated in adolescent migraine, but the high placebo rate resulted in a lack of statistically significant benefit for the primary endpoints in the majority of these studies. The American Academy of Neurology practice parameters for physicians has recommended that ibuprofen and sumatriptan nasal spray are effective, acetaminophen is probably effective, and that they should be considered for the acute treatment of migraine in adolescents [29].

Using a unique method of placebo challenge, nasal zolmitriptan 5 mg was found to be statistically beneficial over placebo in adolescents with rates similar to adults [39•]. Almotriptan 12.5 mg tablet has also recently been demonstrated to be statistically beneficial over placebo in adolescents [40].

In an early intervention open-labeled study with sumatriptan RT 100 mg tablet formulated in 35 adolescent migraine patients, 32 treated at least one migraine attack and 23 treated all four migraine attacks over a 6-month period. The adolescents were instructed to administer within 30 min of attack onset while pain was still mild.

Pain-free response at 2 h postdose (primary endpoint) was reported in 71% of the 112 attacks treated. Migraine-free response (i.e. no pain; no nausea, no vomiting, no photophobia, no phonophobia, and no rescue medication use) at 2 h postdose was reported in 69% of attacks. Response rates were consistent from attack to attack. Rescue medication was used in 19% of migraine attacks. In 112 attacks, a total of 25 adverse events (none serious) were reported in nine patients. The most common adverse events were worsening of symptoms ($n = 5$), neck pain ($n = 4$), and chest tightening ($n = 4$). Early intervention with sumatriptan RT 100 mg tablets constitutes a promising approach to treating migraine in adolescents and warrants a further assessment in controlled clinical trials [41].

There is a lack of placebo-controlled clinical trials for acute, or for that matter preventive, agents among adolescents that have consistently shown statistically significant superiority. This is often explained by the high placebo response rates in adolescents with migraine. Many other factors may play a contributory role: choice of efficacy endpoints, timing of assessments, and time to treatment initiation. To fully determine the clinical benefit of migraine-specific therapies in the setting of adolescent migraine, innovative study designs are needed. A recent study [39•] design built around an initial single-blinded, placebo challenge before patients are randomized to active therapy with an acute agent may be one approach by which this could be achieved. Using such a design with nasal zolmitriptan, the response rate for active medication was similar to adult studies, whereas the placebo rate was much lower than the typical pediatric study.

Although additional unique studies are being designed and performed, we currently must use the results of the available studies, despite their limitations, to help us facilitate the management of pediatric migraine in routine practice [42].

On the very first encounter with pediatric headache patients, it is important to review the pathophysiology of their headache disorder and current headache treatment expectations; this should include a precaution to avoid the overuse of acute medications. Medication overuse or analgesic rebound headaches can frequently lead to an increase in headache frequency and require cessation of acute therapy for recovery.

Preventive medication

When there is an increase in the frequency of three to four migraines per month in the adolescent patient, with increased disability, a preventive therapy plan should be developed. We need to consider three to four migraines per month as the threshold for considering the preventive treatment in young children. Thus, our comprehensive approach may need to include, at least temporarily, preventive medication and biobehavioral management. We need to routinely measure the impact of migraine on the pediatric patient by increasing our use of the assessment tools such as PedMIDAS and PedsQL [5,24,27].

Our goal of preventive treatment is to reduce headache frequency and improve headache disability. Ultimately, the goal is to maintain this reduction at an acceptable level for a long period so that the preventive medication can be discontinued and the biobehavioral therapy alone can sustain this response. Again, there are no absolutes as to what this frequency must be nor for how long, but in general most patients can be successfully weaned off their preventive medication once they are at one to two headaches per month for 3–6 months. This period may be altered based on the school year. Children typically have improved headaches over the summer when they are out of school, so early summer provides an opportunity to reduce medication. Headaches often worsen with the start of school, in late spring and fall; thus, these are less desirable times to discontinue preventive medication.

At present, in the United States, there has not been a single Food and Drug Administration (FDA) approved preventive medication for the treatment of migraine in the pediatric population. Preventive medications are grouped into antiepileptic medications; antidepressant medications [43,44], especially the tricyclic antidepressants; antiserotonergic medications; and antihypertensive medications, including both beta-blockers [45,46] and calcium-channel blockers [29–31,47,48], in adults. The American Academy of Neurology Practice Parameters for physicians has recommended that flunarizine is probably effective for preventive therapy and can be considered for this purpose, but it is not available in the United States [29]. The antiepileptic medications currently being used include divalproate sodium and topiramate (both approved by the FDA for the prevention of migraine in adults) [49,50] and gabapentin, levetiracetam, and zonisamide.

For children, the effective doses for most preventive antiepileptic medications have not been established, but in general the doses should be slowly increased, typically increasing the dose as tolerated over 6–8 weeks, to the lower dosages used for epilepsy [51].

Lewis *et.al.* [52] recently completed a randomized, double-blinded, placebo-controlled, multicenter, 16-week study to evaluate the efficacy and safety of topiramate for the prevention of pediatric migraine. The primary efficacy measure was the percentage reduction in the monthly migraine attack rate compared with baseline. The percentage reductions in the monthly rates of migraine days, headache days, migraine attacks, migraine days with rescue medication, and the 50% responder rate were also evaluated. A total of 106 pediatric patients with migraine with a mean ($\pm$SD) age of 14.2 ($\pm$1.6) years were randomized to topiramate 50 mg/day, topiramate 100 mg/day, or placebo. Topiramate 100 mg/day, but not 50 mg/day, resulted in a statistically significant reduction from baseline ($P = 0.016$) compared with placebo in the monthly migraine attack rate (72.2 vs. 44.4%) during the last 12 weeks of double-blind treatment. In addition, topiramate 100 mg/day, but not 50 mg/day, resulted in statistically significant percentage reductions from baseline compared with placebo in the monthly rates of migraine days ($P = 0.002$), headache days ($P = 0.004$), and migraine attacks (24-h rule: $P = 0.011$; 48-h rule: $P = 0.015$). The 50% responder rate was statistically significantly higher for the topiramate 100 mg/day treatment group compared with placebo ($P = 0.002$). Topiramate

100 mg/day for preventive treatment of migraine was both effective and well tolerated in pediatric patients with migraine [52].

Additional preventive agents may include some nonpharmaceutical treatments and supplements including riboflavin [53,54], coenzyme Q10 [55,56], and butterbur extract [36,57]. Their effectiveness and usefulness in children are yet to be determined.

The key to successful use of preventive medications is to slowly titrate the dose to an effective level. The process requires an understanding by the patient and the parent that it may take several weeks to months before an effective level is achieved, and thus an effective response. The most effective levels have yet to be established in children, although adult guidelines may be useful for adolescents. Nearly one-third of adolescent migraineurs met criteria for preventive therapy, whereas only 19% received it. Prospective studies are needed to fully evaluate the efficacy of preventive management in this population and to establish whether early intervention might slow this disease progression [10].

Biobehavioral treatment

The third component of a comprehensive treatment plan is biobehavioral therapy. This incorporates normalizing a pediatric patient's lifestyle and establishing long-term healthy goals. Biobehavioral therapy can roughly be divided into treatment adherence, lifestyle management, and psychological intervention, including biofeedback assisted relaxation training. Treatment adherence involves educating the patient and the parent about the importance of compliance with their treatment plan and identifying obstacles that may limit the effectiveness of the plan. Adjustment of lifestyle habits includes the identification of triggers for pediatric headaches including inadequate nutrition, skipping meals, and altered sleep patterns. This discussion includes the importance of adequate fluid hydration with limited use of caffeine, regular exercise, and adequate nutrition [58,59]. Additional psychological intervention can include biofeedback-assisted relaxation therapy that has been shown to be effective in the pediatric population [60–63].

Conclusion

Headache/migraine in the pediatric population is underdiagnosed, partly because of different clinical characteristics, compared with migraine in adults. The impact of migraine in adolescents is underappreciated, with children experiencing substantial disability and impaired quality of life.

Advances in the study of pediatric headache disorders have led to an improved recognition of this condition and the understanding of the underlying mechanisms. Given the high prevalence, incidence, and disability of migraine, this recognition needs to be increased to attain improved outcomes and potentially prevent a lifelong impact and disease progression. Once an accurate diagnosis is established, a comprehensive individual treatment plan needs to be developed. Further research is needed to greatly expand our treatment options and develop better long-term outcome measurement tools.

References and recommended reading

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- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 380).

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