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When to Consider Prophylactic Antimigraine Therapy in Children with Migraine

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Abstract

Purpose of review Headache is not an uncommon complaint in children, and recognition of migraine is increasing in children and adolescents. Treatment options consist of abortive and preventive medications; however, when to start the preventive treatment is not clear in the pediatric population. This article reviews current guidelines and practices to provide a better clinical approach in the management of migraines in children and adolescents.
Recent findings Currently, the only FDA-approved medical treatment option for preventive therapy in chronic migraine in adolescents is topiramate. However, the Childhood and Adolescent Migraine Prevention Study (CHAMP) did not endorse superiority of topiramate or amitriptyline over placebo.
Summary At this time, there is no clear consensus on when to start preventive therapy in children and adolescents with migraines. The decision is multifactorial and should be initiated after a thorough discussion with the patient and caregiver(s) about related risks and benefits of treatment. Education regarding various modalities of treatment and ensuring compliance is essential to treatment success.

Introduction

In children, headaches are quite common. Frequently, they are referred to a neurologist's office after receiving thorough workup by their primary care physician for secondary causes such as allergies, vision problems, and sinus problems. Although there has been increased recognition of migraines in children in recent years, it still remains underrecognized and underdiagnosed. Similar to adults, children and adolescents with migraine are often disabled by these headaches. It may lead to increased absence from school and may also affect their attention and participation during studies and other activities. Accurate diagnosis remains elusive due to nonspecific symptoms, poor articulation of symptoms from patients, and lack of recognition of the prevalence of migraine in children/adolescents.

Similar to adult patients with headaches, the evaluation of headache in a pediatric population starts with distinguishing between the likelihood of a primary headache disorder versus a secondary headache disorder. Concern for a secondary etiology is warranted for an initially presenting headache, with adequate workup and assessment required before labeling it as a primary headache disorder. According to the International Classification of Headache Disorders –3, common migraine headaches are at least moderately severe headaches that are frequently throbbing and unilateral, accompanied by nausea, vomiting, photophobia, and phonophobia. The presence of visual or sensory aura distinguishes classical migraine from a common migraine, and the presence of reversible unilateral weakness, dysphasia, or aphasia accompanying headache, not related to other neurological disorders, is diagnostic of hemiplegic migraine [1]. When considering treatment options, it is simplest to classify the various types of migraines as either episodic, frequent episodic (10–14 headache days per month), chronic, or daily [2]. Chronic migraine is described as headaches occurring at least 15 days or more per month for 3 months or more, out of which 8 or more meet criteria for migraine (Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition). This definition of chronic migraine is equally applicable to children and adolescents, and the prevalence of chronic migraine increases with increasing age which is 0.6% in children age 5 to 12 years [3] and 0.8–1.8% in adolescents age 12 to 17 years respectively [4]. Prior to puberty, boys and girls have a similar incidence of chronic migraine [5]. Around the time of puberty, increasing disparity exists between the two groups, with post-pubescent females representing a higher ratio of approximately 3:1 [5, 6].

Early treatment is important for migraineurs in order to prevent the development of refractory or common migraine, and risk factors for chronic migraine include female gender, low socioeconomic status, obesity, medication overuse, insufficient headache relief and prophylaxis, and stress [7]. In this article, we focus on treatment algorithms for children with migraine, with mention of when to consider preventive treatment options.

Goals of prophylaxis

The goal of prevention therapy in migraines is to reduce the frequency and severity of migraine attacks over a period of time [8–10]. Many studies using the SF-26 Health Survey for quality of life show statistically significant improvement across the range of scores with about 6 months of treatment [11] and has also shown to reduce health care costs [12].

It is essential to identify if the headaches are frequent and/or disabling to the degree that patients are willing to commit to a long-term strategic approach, to set appropriate expectations for treatment and response, and to individualize preventive options. Increasing or high frequency, disability, interference with social and educational activities, and co-morbid conditions are reasons for prophylaxis. According to the American Migraine Prevalence and Prevention study, having one or more headache per week is sufficient indication to consider a prophylactic therapy for adults [13] and similar indications should be expected for the pediatric population. With increasing awareness of the risk of

medication overuse headaches in migraineurs, a simple threshold for offering preventive options is if headache treatment is needed more than 6–8 days per month. However, if the level of disability is deemed significant, even with fewer headache days, offering and starting preventive therapies would be warranted. In children and adolescents, disease-nonspecific disability and disease-specific disability have both been demonstrated by Pediatric Quality of Life Improvement (PedsQL) [5, 14, 15], and Pediatric Migraine Disability Assessment (PedMIDAS) [16] respectively. Examples of scenarios that would lower the threshold to start prevention include increasing absence from school (absenteeism), inability to concentrate in school (presenteeism), and development/worsening of other co-morbid conditions such as anxiety, depression, or even suicide ideation in some cases. In children, the duration of headache is often shorter than in the adult population [17]; however, despite having a shorter duration of a headache phase, the level of disability and/or impact is still significant [16]. For instance, even though a migraine headache may last 2 h, the associated pre-monitory/prodromal and posterior wall symptoms may result in a significant decrease in the ability to function in educational and social activities. The impact of frequent/disabling headaches in children often affects the entire family, as parent/guardians often themselves are unable to be productive while tending to the care of these children.

The decision of when to start preventive treatment is predominantly based on the desire/willingness of the patient/caregivers to commit to daily preventive medications. It is commonly encountered that a child or adolescent may have several headaches with disabling features and the clinician feels it is in the best interest of the child to begin preventive therapy; however, initiation of therapy is often not started or delayed due to the caregivers' reluctance. Reluctance to initiate therapy from the caregiver side is multifactorial but often related to concern for potential side effects despite use and even overuse of over-the-counter medications. It is essential to provide appropriate education to both the child and caregivers regarding the effects of untreated migraine, amongst which is medication overuse headache, long-term side effects of over-the-counter medication use, and further progression of the disease. Engaging the patient and family and addressing these matters comprehensively has a higher likelihood of reaching a mutual understanding with appropriate expectations and also provides a clear approach for the clinician in deciding what the appropriate next step is in the preventive care for these children/adolescents. The threshold for offering preventive options should be very low if headaches have reached to the point that a child and/or caregiver has presented to a neurologist's office with a complaint of headache. Had headaches been adequately controlled, children would not likely have been referred.

Treatments

Recognizing the impact associated with migraine necessitates offering an individualized optimal regimen. This includes the utilization of nonpharmacologic measures as well as pharmacologic therapies if needed. Amongst the commonly used nonpharmacologic approaches are biofeedback, relaxation techniques, and cognitive behavioral therapy. As previously mentioned, nonpharmacologic treatment approaches include biofeedback, relaxation techniques,

psychological interventions, and lifestyle modifications. Healthy habits include adequate hydration and sleep, regular meals and exercises, and balanced nutrition. These techniques in general lead to a better coping skill, which results in better overall compliance with treatment efforts and ultimately increased likelihood for successful management of symptoms. Biofeedback therapy has been shown to be very effective in adolescents suffering from migraines [18–20].

Common medications used in migraine prevention include tricyclic antidepressants, antiepilepsy medications, and beta blockers. Nutraceutical options which are also frequently available and used include melatonin, magnesium oxide, riboflavin, and coenzyme Q10. Procedures performed include occipital nerve blocks, sphenopalatine ganglion blocks, and botulinum toxin injections. There are several neuromodulation devices which are FDA approved in adults but have not been approved for use in the pediatric population. Data to support the use of any of these modalities in children is limited, as such, their clinical utility is typically taken from studies performed in the adult population. Because commonly used medications for prevention were not originally designed for the prevention of migraine, the often-guiding factors include possible secondary/multiple benefits from a particular drug and side effect profile. With regard to initial/optimum doses, data is limited for many of the commonly tried adult medications. In the pediatric population, dosing regimens are not clearly established but a general approach with preventive therapies is to start with low doses and to build up if needed and when tolerated. The goal is to reduce the overall frequency and severity of headaches. When deciding to initiate and/or continue approved/off-label preventive therapies, a thorough explanation of the risks/benefits associated with these therapeutic approaches is essential.

FDA-approved treatment options for episodic and chronic migraines are limited, with topiramate being the only shared FDA-approved drug between children and adults [21, 22]. Contrary to the adult migraine populations, the evidence for therapeutic gain compared to placebo is not the same. The CHAMP study assessed the efficacy of topiramate versus amitriptyline versus placebo and suggested that placebo was equally efficacious with less tendency for reported side effects [23•]. However, it is important to note that many perhaps complicated and severe headache cases were excluded from the study. A recent randomized controlled trial compared melatonin and amitriptyline for migraine prophylaxis in children and found them both to be safe and effective [24••]. Amitriptyline was both safer but associated with a higher adverse event rate. In clinical practice, it is observed that many of the standard migraine preventive approaches used in adults are considered in the appropriate context for children/adolescents with migraines. The use of antidepressants, antiseizure medications, nerve blocks, and Botox has all been used off-label in children and adolescents [25–27].

Various factors are taken into consideration such as route of administration, as some children are unable to swallow tablets well, and/or need for supervision, or permission to take medication (i.e., at school). Gabapentin, though not FDA approved for headache, is available in liquid formulation and may be a suitable option to consider in children who are unable to swallow tablets [28]. There is an ongoing investigation into the role of anti-CGRP therapies in children/adolescents [29]. Botulinum toxin, although not FDA approved for use in pediatrics, is often used when other therapeutic measures have not

worked effectively [8, 30]. Although there are limited evidence-based guidelines with regard to the utility of nerve blocks in the preventive treatment of children/adolescents, it is observed that nerve blocks are commonly instituted in practice by providers. Studies have shown that cognitive behavior therapy is effective and should be considered in the preventive treatment plan [18, 20].

One of the hopes perhaps with the CHAMP study was that, potentially, we would gain an idea of which medication between amitriptyline and topiramate would be the optimal medication to try first in the pediatric population. However, the apparent outcome suggested that there is a significant placebo effect in children, such that the choice of medication possibly should be made based on side effect profiles [31]. Further study is required to definitively show improvement with medications over placebo for migraine in children.

Duration, dosages, and adverse events

Prevention should be limited to those patients in whom migraines occur severely or with sufficient frequency. The purpose of therapy is to reduce the frequency, disability, and progression to chronic daily headaches [9]. A usual practice for all preventive medications, especially amitriptyline and topiramate, is to start at a low dose and titrate slowly over 8–12 weeks. Once patient attains a satisfactory response, defined as no more than three headaches per month sustained for at least 4–6 months, these medications can be gradually weaned off. If there is minimal or no response or if side effects occur, a different preventative medication can be tried. Recommended target dose for amitriptyline is 1 mg/kg/day and can be titrated slowly by 0.25 mg/kg for every 2 weeks or more. The effective dose for topiramate for migraine prevention in the pediatric population remains uncertain; various studies suggest a dose from 2 mg/kg/day to 4 mg/kg/day. Doses less than 200 mg/day are recommended [10]. In the CHAMP trial, goal doses of 1 mg/kg and 2 mg/kg for amitriptyline and topiramate were used respectively [23•]. Side effect profiles vary between the two medications: amitriptyline may cause sedation, dry eyes, dry mouth, and weight gain, and topiramate may cause paresthesias, closed angle glaucoma, weight loss, and increased risk of kidney stones. Additionally, topiramate can cause neurocognitive dysfunction [32] as analyzed using the Cambridge Neuropsychological Test Automated Battery: reaction time, pattern recognition, and rapid visual information processing were negatively affected. There were no reports of effects on child's growth and intellect including learning and memory and executive functions [33].

Conclusion

Efforts to start preventive treatment in children should begin with an approach bearing a risk profile similar to placebo. Acceptable practice options include education/awareness of migraine foremost, followed by nonpharmacologic therapies and safer nutraceutical options. If lack of migraine control persists, prescription medications should be tried starting a low dose with slow titration to minimize side effects. Short interval follow-up visits to ensure compliance is recommended.

Engaging the child and caretakers, providing them with appropriate level of education and information of the various modalities and their associated risk

profile, establishing realistic expectations, and stressing adherence and compliance are essential. Individualized treatment plans should be made in consideration of the patient's co-morbid conditions and the patient/caregiver's preferences. With the recent development of calcitonin gene-related peptide antagonist therapies, which seem to have a strong safety profile in adults, it is hoped that these new preventive therapies may have a role in the future management of migraines in the pediatric population.

Compliance with Ethical Standards

Conflict of Interest
Mushtaq Qureshi and Ferhad Bashir each declare no potential conflicts of interest. Gregory Esper reports other from NeuroOne, Inc., outside the submitted work.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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