REVIEW ARTICLE

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Pediatric Migraines: A Comprehensive Review and Perspectives on Diagnosis and Treatment

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ABSTRACT

Pediatric migraine (PM) is one of the most prevalent neurological disorders in children. It has numerous variants and the sufferers often present to emergency departments with a wide variety of signs and symptoms that make diagnosis difficult. The trend in diagnosing and managing PM cases remain suboptimal despite the comprehensive diagnostic criteria and various therapeutic options. In this review, we discuss PM, provide an approach to the diagnosis, and describe the various available management options. However, the diagnosis of migraine is based on history and physical examination; no specific diagnostic test is available. The main management aspects are acute pain relief, prevention, and identifying triggering factors.

Pediatric migraine (PM) is the most severe primary headache in children, leading to decreased quality of life. A migraine episode usually presents as a unilateral headache that increases by physical exertion and is often accompanied by photophobia, phonophobia, nausea, vomiting, and cutaneous allodynia.[1,2] Epidemiological studies show that 7.7% of children develop headaches; among 11- to 13-year-old children, the prevalence of all types of headaches has been estimated to range between 5.9% and 88%.[3,4] The pathophysiological mechanisms underlying migraine in children differ from that in adults due to the continuous neural development in the former.[5] Criteria of the International Headache Society are used to diagnose PM.[6] Recent epidemiological data suggests that 10–20% of school-age children and older adolescents may be suffering from chronic migraines.[7,8]

Based on the presence or absence of aura (sensory abnormalities), PM variants can have a family history of 65–100%.[9] Approximately 61% PM subjects experienced up to three migraine attacks per month.[10] PM and its variants affect children's functioning in school, family, social, and extracurricular activities.[8] Migraine diagnosis is not supported by laboratory or imaging findings but relies on thorough physical examination and history taking. Consequently, the diagnosis of PM is quite challenging.[11] Repeated episodes are often required before a correct diagnosis of PM can be established. Prophylactics such as beta-blockers, calcium channel antagonists, serotonin antagonists, antidepressants, and antiseizure medications have been reported to successfully prevent migraines in children.[12]

Several theories attempt to explain the symptoms of migraine, including the vascular and neurogenic theories.[13] Causal pathways between antagonists and primary headaches and the clinical development of anti-monoclonal therapies are currently under investigation.[14] This review article focuses on the current scientific knowledge regarding PM, its types, diagnosis, red flags, and preventive therapies.

Classification, etiology, diagnosis

CLASSIFYING MIGRAINES BASED ON AURA

There are two primary forms of migraine, which are defined by the presence or absence of certain sensory manifestations—collectively known as 'aura'—in the early stages of headache: migraines with aura (MA) and migraines without aura (MO).[15]

Aura is experienced by about one-third of migraine patients, either during or after each attack. In 90% of these patients, aura manifests in the form of visual illusions, collectively referred to as fortification spectra. Approximately 31% of individuals affected by aura develop sensory symptoms such as pins and needles, numbness, or tingling in the face or arms.[16] Some may experience speech difficulties. The symptoms of aura are fully reversible.

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Those who experience MO may have several (at least five) recurrent episodes of headache, each lasting 4–72 hours. The pain may be moderate or severe, and the attack is usually unilateral, pulsating, and aggravated by routine activities. Photophobia, phonophobia, nausea, and vomiting are common associated symptoms. An attack may be preceded by symptoms such as depression, fatigue, frequent yawning, and food cravings.[16]

Classifying migraines based on chronic symptoms

A primary headache is diagnosed based on criteria developed by the International Headache Society. Their first International Classification of Headache Disorder (ICHD-1) classified migraines into three main cranial neuropathies: primary, secondary, and painful. Primary headache, also known as trigeminal autonomic cephalgia, is a type of cluster headache that is unilateral and with aural fullness. For children, ICHD-1 criteria had limitations. Even though the revised ICHD-2 (2004) introduced tweaks such as reducing the duration of childhood migraine attacks to one hour, many authors considered it unsuitable to diagnose PM.[17]

The new ICHD-3 (beta) has increased the time window of childhood headaches for a diagnosis of PM to 2–72 hours.[15] ICHD-3 also takes cognizance of some factors unique to PM, such as shorter pain durations and unilateral as well as bilateral pain locations.[1,6,18] ICHD-3 classifies chronic primary headaches into four types:

1. Chronic migraine (CM)
2. Chronic tension-type headache (CTTH)
3. New daily persistent headache (NDPH)
4. Medication overuse headache.[6]

A 2019 review of studies on prophylactic therapy of PM observed that when the criteria for the diagnosis of medication overuse was changed, there was an increase of 67.1% in the reported prevalence of CM in a group of 257 children.[6] Using analgesics in patients with CTTH is often ineffective. The male-female difference in the prevalence of CTTH also diminishes to a ratio of 4:5, as opposed to migraine.[4] An NDPH is a headache that appears out of nowhere and lasts more than three months without prior headache history.[19] NDPH also tends to present with features of migraine such as nausea, photophobia, and phonophobia, if ICHD criteria are not followed.[20] As per ICHD-2, a diagnosis of medication overuse headache can be made only if the headache improves after stopping the overused drugs.[15]

Genetic factors

Multiple genes have predisposing roles in the development of migraine. There are also gene-gene interactions, epigenetic variations, and genetic interactions on environmental, nutritional, and behavioral aspects. Such complexity renders it challenging to pinpoint the genomic vulnerabilities in a specific individual's proneness to migraine.[13] Different migraine sufferers may be vulnerable to different ingredients in foods they consume. To prevent migraines, these triggers need to be identified and avoided.[21] An extensive genome-wide association study of patients with headaches found 28 genetic loci related to headaches. Fourteen of these 28 loci were associated with migraines.[22] The term 'epigenetic diet' was coined by Hardy and Tollefsbol[23] to describe how controlling relevant environmental triggers including diet might positively affect one's gene profile and reducing disease risk.[23]

A genetic polymorphism in the STin2 VNTR (variable number tandem repeat) locus may increase migraine risk.[24] A study among 64 nuclear families in Canada found the 5-hydroxytryptamine 1D receptor locus to be linked to migraines with aura.[25] In the same study, transgenic mice exhibited changed behavior and reduction in migraine symptoms associated with female sex hormones. This may help explain the higher prevalence of migraine disorders among females.[26] Specific genes such as *ATP1A2*, *CACNA1A,* and *SCN1A* are involved in a familial hemiplegic migraine, encoded by the Na^+/K^+-ATPase ion transport pump, the Cav2.1 neuronal voltage-gated channel, and the sodium channel voltage-gated Nav1.1 protein, respectively. Mutations in these genes can lead to epilepsy, seizures, neurological disorders, and recurrent coma.[27]

Pathophysiology of migraine

The trigeminovascular (TGV) system has been identified as the primary cause of migraine headaches in studies examining disease etiology.[28] Serotonin depletion, a key factor in the pathophysiology of migraine, is also related to the TGV system.[29,30] Increasing TGV sensitivity and responsiveness are observed in rats with serotonin depletion,

leading to cerebrovascular dilation similar to those associated with migraine in humans.[31] Triptans provide headache relief through increasing serotonin availability.[32] They activate serotonin receptors in cranial nerve endings and blood vessels, causing constriction of blood vessels and limiting peptide release. Thus, triptans are considered a first-line intervention for migraine. However, in trials on children with migraine, triptans have shown even lower effectiveness than placebo.[33–35]

Therefore, adult-specific migraine treatments cannot be expected to be effective in children. This was demonstrated by a clinical trial comparing topiramate, amitriptyline, and placebo which did not indicate any specific effect on migraine frequency.[36] Even though best-practice recommendations for treating headaches in adolescents emphasize a combination of pharmacological and psychological interventions, considerable evidence suggests that the former are not more effective than placebos.[37] A recent review of migraine studies in children and adolescents found that stress, sleep deprivation, weather, video games, and exposure to loud noise as potential triggers for PM.[38]

Diagnostic Criteria

Migraine management requires accurate diagnosis, but several factors limit assessment of headaches in children. The first limitation is the lack of subjective descriptors, particularly in young children. Over the decades, there was an evolution in fixing the criteria of migraine symptoms.[7] As mentioned earlier, ICHD-1 (1988) criteria for diagnosing migraine in children proposed a two-hour headache duration.[1] Subsequently in 1997, Winner et al,[39] proposed a diagnostic criteria for migraine in children and adolescents comprising three points: (1) duration (1–48 hrs), (2) location (bifrontal/bitemporal/unilateral), and (3) accompanying symptoms such as photophobia or phonophobia. Further revisions were made in 2004 (ICHD-2) and the final (current) version being ICHD-3 (2018).

PM has been studied using neuroimaging in several recent studies. In a study of children who suffered from uncomplicated or chronic migraines, computed tomography (CT) or magnetic resonance imaging (MRI) was used to evaluate symptoms.[7] There is no need to image low-risk children with uncomplicated migraines or those who undergo regular neurological examinations. Where imaging is indicated, MRI offers the most cost-effective results.[40] Wang et al,[41] used MRI to reveal abnormalities in four of 688 subjects which CT scans did not show. White matter lesions are significantly more frequent in MA patients than in MO patients.[42] Imaging studies have shown that patients with loss of vision and a history of neurosurgery tend to have significant pathologies. Regular neurological examinations and assiduous history-taking are crucial to diagnosing CTTH. At least four weeks of headache diaries should be kept to facilitate correct diagnosis.[43] If a patient has NDPH, neuroimaging should be performed, specifically gadolinium-enhanced brain MRI and MR or CT venograms.[44]

Red Flags with Migraine Headaches in Children

Results of neuroimaging (brain CT and MRI) of children with headaches must be interpreted cautiously as they often reveal trivial abnormalities causing needless anxiety in patients and their families.[45] Having said that, neuroimaging remains the best method of excluding intracranial pathologies.[46] However, in children with headaches, some emergency clinicians tend to over-recommend urgent neuroimaging when certain warning signs are present, despite limited evidence on its diagnostic utility for such patients.[45] Rho et al,[47] observed that imaging for pediatric headaches, particularly recurring headaches, was quite common, with the most frequent group undergoing unnecessary imaging. Manoyana et al,[48] recently identified four red flag predictors for PM: an abrupt onset (< three months), altered consciousness, focal motor abnormality, and ocular/pupillary abnormality or squint. Children with nontraumatic headaches may benefit from clinical predictor scores based on these four red flags. To validate these red flags, further multicenter prospective studies are needed.

It is critical to seek indicators of increased intracranial pressure such as papilledema, diplopia, extraocular movement abnormalities, and visual field changes.[49] Parents' awareness and attention are crucial in identifying potential red flags such as changes in mood and personality prior to migraine episodes.[48] A sudden onset headache, commonly called a thunderclap headache, is a symptom of reversible cerebral vasoconstriction syndrome. In rare cases, colorful hallucinations as part of MA may also signal underlying epilepsy.[50]

Among 109 children with nontraumatic headaches studied by Manoyana et al,[48] 25.5% were diagnosed with brain tumor, 25.5% had intracranial infections, and 13.7% had intracranial hemorrhage. Among the children aged < 5 years, four out of six were diagnosed with brain cancer, albeit lacking statistical significance due to too few under-five-year-olds in the study. Thus, when a child presents with a chronic nontraumatic headache, the possibility of serious intracranial morbidity should not be ignored. Using the clinical score, physicians can decide whether to refer the patient for specialist consultation and further imaging.[51]

Treatment strategies

Acute migraine is challenging to treat due to high rates of drug nonresponse and difficulties in predicting individual responses to a specific treatment or dose.[52] Abortive and preventive treatments are usually prescribed based on the type of migraine.

Abortive (symptomatic) treatment

Abortive treatment should be given as soon as feasible once pediatric headache symptoms develop,[53] as they are more effective when started an early stage of an episode. Single large doses of medication are more effective than repetitive small doses. Nonsteroidal anti-inflammatory drugs and combination analgesics that combine acetaminophen, aspirin, and caffeine are effective first-line treatments for mild to severe migraine.[54] In a study by Torriero et al,[55] > 80% of children with headaches were diagnosed with primary migraine when the duration criterion of the headache was removed. Thus, monitoring headache duration is important for the correct diagnosis of migraine. Antidepressants, nonsteroidal anti-inflammatory drugs such as paracetamol and ibuprofen, and botulinum toxins have been found effective for CTTH.[43] Due to the variable natural history of NDPH, it is unclear how prophylactic and other treatments will affect its course. The pain of NDPH type of migraine is inexplicably not relieved in numerous patients by any class of abortive or preventive medications.[19] However, drugs such as nortriptyline, topiramate, clonazepam, mexiletine, and gabapentin are suggested for NDPH.[20,44,56] CTTH is most commonly encountered in elementary school-age children and is often accompanied by abdominal pain and anorexia for whom triptans,[49,57] despite being serotonin antagonists, seem to be ineffective. The other most common variant of PM is abdominal migraine characterized by unexplained fever, abdominal pain, anorexia, nausea, and sometimes chronic diarrhea, arthritis, and nocturnal symptoms.[9] Table 1 summarizes the most common medications used for abortive therapy in acute PM.[58]

Preventive treatment

Channel blockers and synthetic drugs

Calcium channel blockers and beta blockers, antihistamines, antidepressants, and antagonists are recommended for preventive therapy to reduce the frequency and severity of migraine.[14] Dihydroergotamine, a synthetic ergotamine, is capable of binding to several serotonin receptors and is used to treat acute migraines. In children, it has been used in hospitals to treat status migrainosus and refractory migraine.[7] Flunarizine blocks calcium

Table 1: Recommended drugs for the treatment of acute pediatric migraine (for emergency department and outpatient settings).[58]

Drug	Dose	Side effects
Ibuprofen, oral	7.5–10 mg/kg, max 800 mg	GI upset, dizziness, GI bleeding
Sumatriptan, nasal spray	5–20 mg (Nasal)	Flushing, dizziness, tightness in the chest or throat
Zolmitriptan (12–17 years)	2.5–5 mg (oral), 5 mg (nasal)	Tiredness, dry mouth, GI upset
Rizatriptan oral (6–17 years)	5–10 mg	Somnolence, nausea, fatigue, and dizziness
Diphenhydramine	1 mg/kg (IV), max 50 mg	Sedation
Magnesium	25–50 mg/kg (IV), max 2 g	Nausea, vomiting, hypotension, flushing
Valproic acid	15 mg/kg (IV), max 1 g	Nausea, vomiting, unsteadiness
Metoclopramide	0.1 mg/kg (IV), max 10 mg	Sedation, extrapyramidal side effects
Prochlorperazine	0.15 mg/kg (IV), max 10 mg	Extrapyramidal side effects, sedation
Dihydroergotamine	0.25 mg (IV), 0.5 mg (IM, SC)	Vertigo, drowsiness

GI: gastrointestinal; IV: intravenous; IM: intramuscular; SC: subcutaneous.

channels in the cerebrovascular system. Al-Qassab et al,[59] reported that flunarizine (2.5–10 mg/day) reduced migraine attack frequency by 50% in 57% of a cohort of children and adolescents of median age 13 years. In a retrospective multicenter study, among migraineurs and CTTH patients, 19% of patients used preventive drugs. For more than half a century, propranolol has served as a migraine prophylactic.[4] In addition to blocking the beta-1,2 receptors, propranolol acts as a nonselective antagonist of beta-adrenoceptors. For migraine prophylaxis in children, Papetti et al,[6] compared propranolol (3 mg/kg/day) with valproate (30 mg/kg/day) and noticed a significant reduction in headache with propranolol in 83% of patients. A study by Richer et al,[60] suggested that propranolol was effective, safe, and tolerable in treating monthly headache frequency by 68% in their study population. Serotonin modulators such as pizotifen (1.5 mg/day) and cyproheptadine (0.2–0.4 mg/kg/day) were also found to be effective prophylactics. However, side effects such as weight acquisition, increased appetite, drowsiness, and sedation were observed.[6] The most commonly used medications for prophylaxis in the treatment of PM are shown in Table 2.

Multidisciplinary interventions have been recommended to reduce migraine disability, improve coping strategies, and reduce the risk of chronification of pain in children.[21] Among these are psychological methods such as behavior therapy, reported to offer both prophylactic and therapeutic benefits.[61] In 15 randomized clinical studies of behavioral therapies for chronic pain in PM, Fisher et al,[62] reported that such interventions substantially diminished headaches. Cognitive behavior therapy (CBT) has been indicated to reduce the number of CM episodes. The effectiveness of CBT in children can be enhanced by coopting acceptance and commitment therapy and mindfulness meditation.[63] Such options may be tailored to each child based on clinical evidence and individual preferences.[2]

Neuromodulation

Neuromodulation (NM) involves altering the natural transmission of nerve impulses by means of drugs or surgical procedures.[64] NM is a rapidly developing area of research for managing headache pain by modulating neural regions associated with the pathophysiology of migraine.[65] To improve neuronal function and help treat pathological conditions including pain and mobility problems, NM combines biomedical engineering with neurophysiology.[66] A new NM device, noninvasive transcutaneous supraorbital neurostimulator Cefaly® device that stimulates the TGV system has gained popularity among headache patients, and a follow-up investigation among 2313 patients suggested it to be safe and well-tolerated.[67] Another device, Spring TMS (single-pulse transcranial magnetic stimulator), was found effective in 12-year-old children with PM, albeit with mild side effects such as light-headedness.[68]

Emerging serotonin antagonists

Some recently developed antagonists, such as angiotensin, serotonin, and calcitonin gene-related peptide (CGRP) are found to be effective in reducing symptoms of PM.[14] In the PIONEER-PEDS1 and PEDS2 trials, 5-HT 1F receptor agonist lasmiditan (a serotonin antagonist) was beneficial for PM in both

Table 2: Commonly used drugs for prevention of migraine headaches in children.[58]

Drug (class)	Dose	Side effects
Propranolol (Non-selective beta-adrenoceptor antagonist)	3 mg/kg/day	Nausea, vomiting, diarrhea, fatigue
Flunarizine (Calcium channel blocker)	5–10 mg/day	Weight gain, sedation, depression
Topiramate (Antiseizure medication)	2–3 mg/kg/day	Dizziness, anorexia, cognitive dysfunction
Amitriptyline (Tricyclic antidepressant)	1 mg/kg/day	Sedation, dizziness, constipation, weight gain
Pizotifen (Serotonin modulator)	1.5 mg/day	Weight gain, drowsiness, dry mouth
Cyproheptadine (Antihistamine)	0.2–0.4 mg/kg/day	Drowsiness, fatigue, weight gain
Sodium Valproate (Antiseizure medication)	30 mg/kg/day	Nausea/vomiting, alopecia, weight gain
Riboflavin (Nutraceutical)	400 mg/day	Diarrhea
Coenzyme Q10 (Nutraceutical)	150–300 mg/day	Nausea, vomiting, heartburn, loss of appetite
Butterbur root (Nutraceutical)	100–150 mg	Belching, diarrhea, drowsiness, hepatic toxicity

adults and children. Gpants (a CGRP agonist similar to eptinezumab, fremanezumab, and galcanezumab) is reported to be effective in chronic PM.[69,70] A new era has begun in the emergency and preventive treatment of primary headache diseases with the discovery of anti-CGRP medications. Recently, it was reported that activation of TGV system is mediated by CGRP release, providing a new insight into migraine pathophysiology.[71] Altering CGRP or its receptor would alter its gene expression; thus, revealing another strategy to treat migraine through genetic manipulation.[71] The potential of these emerging therapies are encouraging.

CONCLUSION

We discussed PM and the current developments in its diagnosis and management, including the emerging ones. Once diagnosed, migraines in children can be managed acutely and preventively with a variety of therapies. As of now, a step-by-step approach is considered the best method of providing individualized therapy. An abortive treatment option can be offered to use for patients when a migraine attack occurs. It is also essential to guide the affected children and their families to adopt healthy lifestyle habits. Research on preventive treatments for PM is still limited. However several new methods are either already introduced or in research stages, including newer channel blockers, neuromodulation, and genetic interventions. Also, showing promise are psychological interventions such as CBT.

Disclosure

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