Pediatric Migraines: A Comprehensive Review and Perspectives on the Diagnosis and Treatment of Migraine

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Abstract

Paediatric migraines (PMs) are one of the most prevalent neurological disorders, with numerous variants, including abdominal migraine, cyclic vomiting, and paroxysmal torticollis. Children with headaches often visit emergency departments with some worrisome signs that make diagnosis difficult. The diagnosis, and clinical management of migraine remain suboptimal despite the comprehensive diagnostic criteria and various therapeutic options. Clinicians depend on their knowledge of pertinent red flags, together with other diagnostic methods, to arrive at a clinical diagnosis of PM. During the last five years, migraine therapy has advanced dramatically, with innovative mechanism-based medicines that complement the standard of care and reduce the clinical burden. Additionally, genetic factors can determine patients' vulnerability to migraine in numerous cases. Not all PM subjects benefit from abortive and prophylactic treatments, including triptans, antiseizure medications, and NSAIDs (nonsteroidal anti-inflammatory drugs). Recently, the use of monoclonal antibodies, such as calcitonin gene-related peptide (CGRP) receptor and serotonin antagonist, and neuromodulation has attracted attention in the treatment of PM. Additional validation studies are needed to aid in patient referral, enhanced neuroimaging, and effective therapy among PM subjects. The necessity for cost-effective techniques and efficacy among multi or interdisciplinary PM treatments on a massive scale is needed.

Keywords: Paediatric migraine, nonsteroidal anti-inflammatory drugs, calcitonin gene-related peptide (CGRP) receptor, red flags, triptans, abortive treatment, preventive treatment

Introduction

Migraine is a severe and debilitating disease with a chronic neurological effect, especially in children. Usually, present as a unilateral headache increased by physical exertion, with photophobia, phonophobia, nausea, vomiting, and cutaneous allodynia (1, 2). Epidemiological studies show that 7.7% of children develop headaches, with a prevalence range of 5.9 to 88% of 11- to 13-year-old children (3, 4). Due to continuous neural development, the pathophysiological mechanism underlying migraine in children differs from adults (5). Migraine is the most devastating primary headache in children and is associated with a decreased quality of life (QoL). Based on the symptoms, the International Headache Society (IHS) criteria are followed for the diagnosis of PM (6). The epidemiological data of recent years have substantiated the plight of PM (7). Approximately 10 to 20% of school-age children and older adolescents suffer persistent migraines, which are chronic (8).

Based on the aura and without aura (sensory abnormalities), PM variants have been described, which include periodic syndrome, abdominal migraine, vertigo, cyclic vomiting, and paroxysmal torticollis, with a family history of 65-100% (9). Most PM subjects, approximately 61%, experienced >4 migraine attacks per month (10). PM and its variants affect children's school, family, extracurricular, and social functioning (8). Migraine diagnosis is not supported by laboratory or imaging findings but relies on a thorough physical examination and history. Hence, the diagnosis of PM is quite challenging (11). Repeated episodes are often required before a correct diagnosis of PM is established, which is often a burden for patients and their family members. Children demonstrated success with migraine prophylaxis using medications such as beta-blockers, calcium channel antagonists, serotonin antagonists, antidepressants, and antiseizure medications (12). Several theories attempt to explain the symptoms of migraine, including the vascular and neurogenic theories (13). Establishing causal pathways between

antagonists and primary headaches and the clinical development of anti-monoclonal therapies is an example of translational research and is under investigation (14). The current review article focuses on the knowledge of PM, its types, diagnosis, preventive therapies, and red flags.

Current knowledge of paediatric migraine

Classification of migraine based on aura

There are two primary forms of migraine, which are defined by a range of sensory abnormalities (called an aura) that might occur in the early stages of the headache: migraines with or without aura (MA or MO, respectively) (15).

Migraines with aura (MA)

The aura is experienced by approximately one-third of migraine patients, either during or after each attack. Aura manifests visually in >90% of affected individuals and is traditionally used as fortification spectra. Approximately 31% of individuals with this condition develop sensory symptoms such as pins and needles, numbness, and/or tingling in their face or arms (16). The patient may experience visual sensory, retinal and speech reversible aura symptoms.

Migraines without aura (MO)

Those who have migraine without aura experience recurrent headache attacks (minimum 5 attacks) that last between 4 and 72 hours. Pain may be moderate or severe, and the attack is usually unilateral, pulsating, and aggravated by routine activities. Photophobia, phonophobia, nausea, and vomiting are commonly associated symptoms. Symptoms that precede pain include depression, fatigue, yawning, and food cravings (16).

Classification of migraine based on chronic symptoms

A primary headache is diagnosed based on criteria developed by the International Headache Society (IHS). In the paediatric age group, these criteria have shown limitations. The International Classification of Headache Disorder (ICHD) has classified migraines into three parts, as part one, two, and three, which mainly include primary, secondary, and painful cranial neuropathies, respectively. Primary headache is a cluster headache type that is unilateral and aural fullness. It is also known as trigeminal autonomic cephalgias (TACs). In 2004, ICHD 2 reduced the duration of migraine attacks on children to one hour. However, many authors believe that ICHD 2 is still unsuitable for diagnosing primary headaches in children (17). In case of PM, the children now have a longer window of 2 to 72 hrs before being diagnosed with migraine, according to changes made in the third beta version of ICHD 3 (15). To define the prognosis and provide treatment, early diagnosis is essential.

However, ICHD 3 considers some unique factors in PM, such as shorter pain durations and unilateral/bilateral pain locations (6, 18, 19).A child's QoL deteriorates dramatically when they suffer from chronic primary headaches (CPHs) and can be classified into four types based on ICHD 3:

i) Chronic migraine (CM)

ii) chronic tension-type headache (CTTH) and

iii) new persistent daily headache (NDPH)

iv) Medication overuse headache (MOH) (6).

According to Papetti et al., (6) an increase in the prevalence of CM of 67.1% was observed in 257 patients when their overused medication diagnosis was changed. Using analgesics in patients with CTTH is often ineffective. As opposed to migraine, there is only a slight difference in the prevalence of TTH in women and men, a ratio of 5:4 (4).An NDPH is a headache that appears out of nowhere and lasts more than three months without prior headache history (20). There is a high incidence of migraines features associated with NDPH if ICHD criteria

are not followed, including nausea, photophobia, and phonophobia (21). ICHD 2 states that a diagnosis of patients with MOH can only be made if the patient's headache improves after the removal of overused drugs and is often associated with primary headache (15).

Genetic factors

Multiple genes play a role in the development of migraine, along with external factors, including gene–gene interactions, epigenetics, and environmental and nutritional aspects of genes. It is challenging to pinpoint relevant genomic risk factors in migraine because it exhibits differences from person to person (13). Genetic factors can also act as predisposing factors. Different food ingredients can affect some people, and certain beverages can affect others. To prevent migraines, these triggers should be avoided (22). An extensive genome-wide association study of patients with headaches found 28 genetic loci related to headaches. It was reported previously that 14 of these 28 loci were associated with migraines (23). The term "epigenetic diet" was coined by Hardy and Tollefsbol (24). to describe how environmental factors, such as dietary factors, can positively affect an individual's gene profile, thus preventing disease.

It has been proposed that a genetic polymorphism in the STin2 VNTR (variable number tandem repeat) locus may increase migraine risk (25). In a study of 64 families by Thompson et al., (26). discovered that the 5-HT1D receptor locus was linked to MA. In the same study, transgenic mice have also been shown to exhibit changed behavior and improve migraine symptoms due to female sex hormones. The prevalence of migraine disorders among females may be explained by the abovementioned reason (27). Specific genes such as *ATP1A2*, *CACNA1A*, and *SCN1A* are involved in familial hemiplegic migraine (FHA), 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 lead to epilepsy, seizures, neurological disorders, and recurrent coma (28).

Pathophysiology of migraine

Migraines have a complex pathophysiology that is only partially understood. The trigeminovascular (TGV) system has been identified as the primary cause of migraine headaches in studies examining disease etiology (29). Serotonin is one mechanism underlying the pathophysiology of migraine, which is also related to the TGV system (30, 31). Increasing TGV sensitivity and responsiveness are observed in rats with serotonin depletion, enhancing cerebrovascular changes (32). In PM trials, triptans have shown low effectiveness compared to placebo despite being considered a first-line intervention (33–35). Triptans constrict blood vessels and limit peptide release by activating serotonin receptors in cranial nerve endings and blood vessels. Therefore, it improves pain relief effects through serotonin (36). The response to antipsychotic treatment has been linked to variations in serotonergic genes (HTR2A, SERT), which are targeted by a number of medicines besides triptans (37).

Adult-specific treatments might not be effective in children, as a clinical trial comparing topiramate, amitriptyline, and placebo did not indicate any specific effect on migraine frequency (38). Even though best-practice recommendations for treating headaches in adolescents emphasize a combination of pharmacological treatment and psychological intervention, considerable evidence suggests that the former are not more effective than placebos (39). In addition to pharmacological drugs, several nonpharmacological factors have been identified for PM. Recent reviews have found that stress, sleep deprivation, weather, video games, and loud noise contribute to anxiety (40).

Diagnostic criteria

Migraine management requires an accurate diagnosis, but several unique factors limit children's headache assessment. The first issue is the lack of subjective descriptors, particularly in young children. There is also a noticeable change in migraine symptoms (7). In the first edition of the ICHD criteria for diagnosing migraine in children, a 2-hr duration was proposed (1). Winner et al. (41) developed a new category for migraine in children and adolescents. There are three factors to consider:

1) the duration of time (1-48 hrs);

2) the location (bifrontal/bitemporal/unilateral) and

3) accompanying symptoms (such as photophobia or phonophobia).

PMs have been studied using neuroimaging in several recent studies. In a study of children who suffered from uncomplicated migraines or CM, computed tomography (CT) or magnetic resonance imaging (MRI) was used to evaluate the children's symptoms (7). There is no need for imaging in low-risk children (uncomplicated migraines and regular neurological examinations). In cases where imaging is indicated, magnetic resonance imaging offers the best cost-effective outcome while maximizing QoL expectancy (42). According to Wang et al., (43) magnetic resonance imaging revealed abnormalities in 4 of 688 subjects; however, CT scans did not indicate significant abnormalities. White matter foci are significantly more frequent in MA patients than in MO patients (44). Patients with migraines and normal subjects have frequent abnormalities on their magnetic resonance and computed tomography scans. Imaging studies have shown that patients with loss of vision and a history of neurosurgery have significant pathologies. Regular neurological examinations and the patient's history are crucial to diagnosing TTH. At least four weeks of headache diaries should be kept to ensure a correct diagnosis (45). If a patient has NDPH, neuroimaging should be performed, specifically gadolinium-enhanced brain MRI and MR or CT venograms (46). Neuroimaging has the potential to reveal trivial results that cause needless anxiety in patients and their families (47).

Red flags with migraine headaches in children

Clinicians seem to recommend urgent neuroimaging when certain warning signs are present in children with headaches. However, there is limited evidence on the use of neuroimaging in emergency departments (47). The earliest neuroimaging (brain CT and MRI) is the best method of excluding intracranial pathologies and is essential to guide treatment (48). However, neuroimaging in children with headaches can be overused due to nonspecific red flag indications and the rarity of clinically relevant intracranial lesions. (47). An abrupt onset (< 3 months), altered consciousness, focal motor abnormality, and ocular/pupillary abnormality or squint were recently identified as four warning red flag predictors by Manoyana et al. (49).

It is critical to seek indicators of increased intracranial pressure, such as papilledema, diplopia, extraocular movement abnormalities, and visual field changes (50). Parents' perception and attentiveness of their children's monitoring are crucial in identifying some red flags, such as mood or personality changes (49).Rho et al., (51). observed that imaging for paediatric headaches, particularly recurring headaches, was quite common, with the most frequent group undergoing unnecessary imaging. A sudden onset headache, commonly called a thunderclap headache, is a symptom of reversible cerebral vasoconstriction syndrome. Visual symptoms can be associated with migraine aura; however, children experiencing colourful hallucinations may have a rare diagnosis of epilepsy (52). There were only six patients younger than five years of age in a study by Manoyana et al., (49). Since the number of patients in this age group is small, the 5-year cut-off point did not reach statistical significance. However, most of them had been diagnosed with brain cancer. When patients present with a nontraumatic headache, the emerging intracranial lesion remains a concern. Using the clinical score, physicians can select the patient to refer for specialist consultation and further imaging to the tertiary care centre (53).Paediatric patients with nontraumatic headaches may benefit from clinical predictor scores based on these four red flags. For the validation of red flags and improvement of clinical prediction scores, further multicentre prospective studies are needed.

Treatment strategy

Acute migraine is challenging to treat due to high rates of drug nonresponse and difficulties in predicting individual responses to a single treatment or dose (54). 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 after developing symptoms (55). Abortive treatments work better when started early in headaches. Single large doses are more effective than repetitive small doses of medication. Nonsteroidal anti-inflammatory drugs (NSAIDs) and combination analgesics that combine acetaminophen, aspirin, and caffeine are effective first-line treatments for mild to severe migraine (56). Whenever a migraine attack begins, simple analgesics must be administered as soon as possible. A study by Torriero et al., (57). suggested that more than 80% of children with primary migraine are diagnosed when the duration criteria of the headache are removed. Comorbidities should be considered when treating CTTH; antidepressants, NSAIDs

(such as paracetamol and ibuprofen), and botulinum toxins were effective when treating TTH (45). It is unclear how prophylactic and other treatments will affect the natural history of NDPH due to its variable natural history. The pain of numerous patients suffering from NDPH is inexplicably not relieved by any class of abortive and preventive medications (20). Drugs including nortriptyline, topiramate, clonazepam, mexiletine, and gabapentin may effectively treat the NDPH type of migraine. (21, 46, 58). Triptans (a serotonin antagonist) have been reported to not play a role in reducing the symptoms of CTTH. It is most commonly encountered in elementary school-age children and is often accompanied by abdominal pain and anorexia (50, 59). The other most common variant of PM is abdominal migraine (AM) with unexplained fever, abdominal pain, anorexia, nausea, and sometimes chronic diarrhoea, arthritis, and nocturnal symptoms (9). There has been a recommendation for multidisciplinary interventions to reduce migraine disability, improve coping strategies, and reduce the risk of chronification in children with migraine. Table 1 summarizes the most common medications used for abortive therapy in acute PM.

Table 1: Acute treatment of migraine (In emergency department and outpatient settings).

Drug	Dose	Side effects
Ibuprofen, oral	7.5-10 mg/kg, max 800 mg	Gastrointestinal (GI) upset, dizziness, GI bleeding
Sumatriptan, nasal spray	5 to 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, Intravenous (IV), max 50 mg	Sedation
Magnesium	25 to 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

Preventive or prophylactic treatment

Channel blockers and synthetic drugs

Calcium channel and beta blockers, antihistamines, antidepressants, and antagonists are recommended for preventive therapy to reduce the frequency and severity of migraine (14). Synthetic ergotamine called dihydroergotamine (DHE) has an affinity for several serotonin receptors and is used to treat acute migraines. In children, it has been used to treat status migrainosus and refractory migraine in hospitals (7). Flunarizine blocks calcium channels in the cerebrovascular system. According to Al-Qassab et al., (60) flunarizine (2.5–10 mg/day) reduces attack frequency by 50% in 57% of children and adolescents (median age 13 years). In a retrospective multicentre study, among migraineurs and TTH patients, 19% used preventive drugs. In addition to blocking the b1,2 receptors, propranolol acts as a nonselective antagonist of beta (b) adrenoceptors. More than 50 years ago, propranolol has been used for migraine prophylaxis (4). 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 among 83% of patients with propranolol. A study by Richer et al., (61) suggested that the beta-blocker propranolol is effective, safe, and tolerable in treating monthly headache frequency by 68%. Serotonin modulators such as pizotifen and cyproheptadine were also found to be effective in reducing migraine symptoms when doses of 1.5 mg/day and 0.2-0.4 mg/kg/day, respectively, were recommended. 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.

Table 2: Commonly used drugs for prevention of migraine headaches in children:

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

Psychological or behavioural therapy

Using pharmaceuticals and nonpharmacological interventions has proven to be both practical and widely available (62). In 15 randomized clinical studies of behavioural therapies for chronic pain in PM, Fisher et al., (63). reported that such interventions substantially diminish headaches. In children with CM, cognitive behavioural therapy (CBT) has been indicated to reduce the number of episodes of headaches. People living with migraine may benefit from additional or alternative psychological therapies, such as acceptance and commitment therapy (ACT) and mindfulness-based techniques, to improve the effectiveness of CBT (64).Treatment options may be tailored to each individual based on clinical evidence and individual preferences (2). Migraine can be treated acutely and preventively with a variety of effective therapies. Patients should receive the best therapy for their individual needs when choosing between these therapies. Unfortunately, there is no prior basis for selection, at least for acute therapy. Therefore, a step-by-step approach to therapy is considered the best method of providing individualized therapy (16).

Neuromodulation (NM)

Neuromodulation is changing the transmission of nerve impulses using methods other than the nerves, such as through drugs or surgical procedures (65). NM is a rapidly developing area of research for managing headache pain by modulating neural regions that are often associated with the pathophysiology of migraine (66). To improve neuronal function and help treat pathological conditions, including pain and mobility problems, NM combines biomedical engineering with neurophysiology (67). Currently, a noninvasive transcutaneous supraorbital neurostimulator (tSNS) Cefaly® device that stimulates the TGV system is used, and a follow-up investigation among 2,313 patients suggested that NM is safe and well tolerated (68). Another device, Spring TMS (single-pulse transcranial magnetic stimulator), was influential in children 12 years of age with mild side effects, such as light-headedness (69).

Recent antagonists (new era medicines)

Some antagonists, such as angiotensin, serotonin, and calcitonin gene-related peptide (CGRP), have been recently developed and are effective in reducing PM-associated symptoms (14). In the PIONEER PEDS-1 and PEDS-2 trials, the 5-HT 1F agonist lasmiditan (a serotonin antagonist) was beneficial in treating PM in both adults and children. Similarly, GPANTS (a CGRP agonist like eptinezumab, fremanezumab, and galcanezumab) is effective in the treatment of chronic PM (70, 71). Recently, it was reported that activation of TGV system is mediated by CGRP release, providing migraine pathophysiology and thus delivering new antimigraine drugs (72). In the same study, it was explained that altering CGRP or its receptor would alter its gene expression and is considered another strategy in the treatment of migraine through genetic manipulation. A new era has begun in the emergency and preventive treatment of primary headache diseases with the discovery of anti-CGRP medications. PM sufferers may take monoclonal antibody or antagonist therapies, but this will depend on their accessibility and affordability. The potential benefits of existing therapies are encouraging.

Conclusions

It is possible to successfully treat headaches with a wide range of therapeutic choices, but numerous hurdles remain, such as a lack of understanding of specific patient therapy. Following a proper diagnosis, it is essential to guide patients and their families on healthy lifestyle habits. An abortive treatment option can be offered to patients when a migraine attack occurs. Where headaches occur frequently or negatively impact QoL, prevention therapy may be necessary. Research on preventive treatments for children has been limited, and most of our practices are based on adult studies. Chronic, frequent, or severe headaches affect daily activities and warrant prophylactic treatment with an anti-inflammatory drug. Especially in PM treatment, these avenues deserve further clarification.

Additional validation studies are needed to aid in patient referral, enhanced neuroimaging, and effective therapy among PM subjects.

Conflict of interests

The author claims no conflict of interest and no financial support.

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