Introduction

Headache is one of the most common complaints encountered in children and adolescents, often leading to outpatient and emergency visits [1]. The primary task for a pediatrician or pediatric neurologist in headache evaluation is to differentiate the small fraction of children with secondary headaches from the majority who have a primary headache disorder, such as migraine. The initial steps in evaluation involve a thorough history, general physical examination, and complete neurological assessment. If the initial assessment raises suspicions of a secondary etiology, additional diagnostic testing, including neuroimaging and cerebrospinal fluid (CSF) examination, may be necessary in some cases.

Epidemiology and Etiology

Studies evaluating the prevalence of headache in children have reported substantial variation, with prevalence rates ranging between 8% and 88% in children [2]. A meta-analysis found the prevalence, assessed at intervals from 1 month and the lifetime, was 58.4% in children and adolescents [3]. In a study of American children, 17.1% reported experiencing frequent or severe headaches, including migraines, within the last 12 months. The occurrence of headaches rises with age, reaching a prevalence rate of up to 27% among 16- to 18-year-olds. Sex variations in headaches become noticeable after puberty, as girls demonstrate a higher prevalence rate than boys [4]. Headaches occur more frequently in children with a positive family history [5-7]. The overall estimated prevalence of migraine is around 8% in children, assessed over a period between 6 months and the lifetime [3].

1. Etiology

Headaches in children can be categorized into primary, where pain is a result of the headache condition itself, and secondary, where
pain serves as a symptom of an underlying condition. Migraine and tension-type headaches are the most frequently encountered types of primary headaches in children [8]. Cluster headache, a type of primary headache in children, exhibits similar characteristics to headaches in adults but is rare among young children [9]. Upper respiratory tract infections are the commonest cause of secondary headaches that prompt emergency visits. Meningitis, hydrocephalus, and intracranial tumours are common etiologies of life-threatening headache in children [10]. Frequently, no diagnosis can be reached despite an extensive evaluation. In a study involving 48,575 children aged 5 to 17 years who had headache disorders, about 19% were identified with primary headaches, 1.1% were diagnosed with secondary headaches, and 79.7% did not receive a formal diagnosis [11].

2. Pathophysiology
The pathophysiology of headaches is intricate, with genetic and environmental factors playing crucial roles in the development of migraine, tension-type headache, and cluster headache. However, identifying the specific genes involved has proven to be a challenging task. Familial hemiplegic migraine, which is linked to mutations in the calcium voltage-gated channel subunit alpha 1 A (CACNA1A), ATPase Na+/K+ transporting subunit alpha 2 (ATP1A2), and sodium voltage-gated channel alpha subunit 1 (SCN1A) genes, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is associated with a notch receptor 3 (NOTCH3) gene mutation, stand out as the most extensively studied headache disorders with a genetic foundation [12].

The vascular theory of migraines, according to which migraine stems from blood vessel dilation and that the aura is a result of vasosconstriction, is now deemed invalid, as evidenced by magnetic resonance angiography studies [13]. A typical migraine episode consists of four phases: the prodromal or premonitory phase, the aura phase, the headache phase, and the post-dromal phase [14]. The premonitory phase is characterized by irritability, fatigue, difficulty in concentration, nausea, or pallor. Functional neuroimaging studies suggest involvement of the hypothalamus in the premonitory phase, as well as during the migraine attack phase [15]. The migraine aura constitutes a reversible neurological phenomenon impacting approximately one-third of all migraine sufferers and occasionally overlapping with the headache phase. The underlying mechanism of this phase is thought to involve cortical spreading depolarization (CSD) across the cortex. CSD is marked by a brief excitation period, followed by a prolonged depression of cortical activity. Originating from the occipital lobes, it propagates anteriorly, dissipates at the central sulcus, and influences neurotransmitter levels, ionic balance, and blood flow [16]. The headache phase is characterized by the activation of the trigemino-cervical complex. Neuropeptides, particularly calcitonin gene-related peptide (CGRP), are involved in trigeminal activation and have emerged as a potential target for therapeutic interventions in migraine patients [15]. A simplified overview of the pathophysiology of migraine is depicted in Fig. 1.

The development of cluster headaches involves interactions among the trigemino-vascular pathway, trigeminal autonomic reflex, hypothalamus, and the neuropeptides CGRP and pituitary adenylate cyclase-activating polypeptide [17]. In tension-type headaches, the pain is thought to stem from myofascial structures and is heightened by central sensitization mechanisms. This central sensitization involves an imbalance in neurotransmitters such as CGRP, nitric oxide, neurokinin-A, glutamate, substance-P, serotonin, and endogenous peptide systems [18].

Classification
The International Classification of Headache Disorders, third edition (ICHD-3) provides comprehensive criteria for diagnosing primary headaches, secondary headaches, neuropathies, and facial pain disorders [19]. It is important to note that primary and secondary headaches are not mutually exclusive; individuals with a primary headache may experience a headache that is exacerbated by a cause of secondary headaches.

1. Primary headache
The most prevalent types of primary headaches in children are migraine and tension-type headaches. Cluster headache is a type of trigeminal autonomic cephalalgia and is relatively rare in children.
1) Migraine
In children, migraine diagnosis adheres to the criteria for migraine in adults as outlined in ICHD-3, albeit with some distinctions related to symptom duration and location. While migraine in adults typically lasts for 4 to 72 hours (when not treated or unsuccessfully treated), the duration in children can be as short as 2 hours. Headache is more often bilateral in children as compared to adult population; the pattern of unilateral pain often emerges during late adolescence or early adulthood. The photophobia and phonophobia may be evident based on the behavior of young children [19]. Children and adolescents, like adults, also undergo the premonitory and postdrome phases. Premonitory symptoms are observed in up to two-thirds of adolescents and include fatigue, irritability, mood changes, yawning, alterations in urination patterns, neck stiffness, sensitivity to light, nausea, and facial pallor or dark circles around the eyes [20]. Recognizing premonitory symptoms can be advantageous for the early identification and management of migraine attacks. After the headache phase, children may also manifest a post-dromal phase. In a study, 82% of patients reported a post-headache phase characterized by symptoms such as thirst, excessive somnolence, visual blurring, and food cravings [21]. The diagnostic criteria for migraine headaches are shown in Table 1.

The ICHD-3 recognizes a cluster of conditions usually observed in childhood and potentially linked to an elevated risk of developing migraine. There is evidence indicating that these conditions may serve not only as precursors but also as manifestations of migraine [22]. Diagnosing episodic syndromes relies on a thorough clinical evaluation and the exclusion of alternative diagnoses. Some metabolic disorders featuring episodic vomiting and seizure disorders can mimic these episodic syndromes, emphasizing the need for careful consideration and differential diagnosis. These episodic syndromes are summarized in Table 2 [23-28]. In the ICHD-3 classification, infantile colic and alternating hemiplegia of childhood are included in the appendix of ICHD-3 but not in the text.

2) Tension-type headache
Tension-type headache is categorized as a primary headache disorder, presenting as a diffuse pain characterized by a pressing or tightening sensation. The diagnostic criteria of tension-type headache are summarized in Table 3. The severity typically ranges from mild to moderate, and it is not aggravated by physical activity. While it may be accompanied by photophobia or phonophobia, nausea and vomiting are not typically observed. Tension-type headache is further classified as infrequent, frequent and chronic based on the frequency of the headache according to the ICHD-3 classification [19].

3) Cluster headache
Cluster headache is a type of trigeminal autonomic cephalalgia. It is characterized by intense to extremely severe pain located in the frontal or orbito-frontal region, accompanied by autonomic features including conjunctival injection, rhinorrhoea, or sweating. The diagnostic criteria of cluster headache are summarized in Table 3. Cluster headache is rare in children.

The clinical characteristics of migraine, tension-type headache, and cluster headache are summarized in Table 4 [29].

2. Secondary headache
Secondary headaches are caused by an underlying condition. This term includes cases where a primary headache is exacerbated by an underlying condition. Common causes of secondary headaches include central nervous system infections, trauma, stroke, idiopathic intracranial hypertension, hypertension, and pain arising from the ear, cranium, eye, neck, nose, sinus, teeth, or other local involvement [19].

Table 1. The ICHD-3 diagnostic criteria of migraine in children

<table>
<thead>
<tr>
<th>Migraine without aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Minimum 5 headache attacks that fulfill the criteria 2 to 4.</td>
</tr>
<tr>
<td>2. Headache attack lasting for 2–72 hours.</td>
</tr>
<tr>
<td>3. Headache has at least two out of the four following characteristics:</td>
</tr>
<tr>
<td>Unilateral in location</td>
</tr>
<tr>
<td>Pulsating nature</td>
</tr>
<tr>
<td>Moderate or severe headache in intensity</td>
</tr>
<tr>
<td>Aggravated during physical activity or headache leads to avoidance of physical activity</td>
</tr>
<tr>
<td>4. At least one of the following characters during the headache:</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
</tr>
<tr>
<td>Photophobia and phonophobia</td>
</tr>
<tr>
<td>5. Not explained by an alternative ICHD-3 diagnosis</td>
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<table>
<thead>
<tr>
<th>Migraine with aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Minimum 2 attacks fulfilling criteria 2 and 3</td>
</tr>
<tr>
<td>2. One or more of the following reversible aura symptoms:</td>
</tr>
<tr>
<td>Motor</td>
</tr>
<tr>
<td>Sensory</td>
</tr>
<tr>
<td>Visual</td>
</tr>
<tr>
<td>Speech and/or language</td>
</tr>
<tr>
<td>Brainstem</td>
</tr>
<tr>
<td>Retinal</td>
</tr>
<tr>
<td>3. At least three of the following six characteristics:</td>
</tr>
<tr>
<td>At least one aura spreads gradually over 5 minutes</td>
</tr>
<tr>
<td>2 or more aura symptoms occur in succession</td>
</tr>
<tr>
<td>Each aura symptom lasts 5–60 minutes</td>
</tr>
<tr>
<td>At least one aura symptom is unilateral</td>
</tr>
<tr>
<td>At least one aura symptom is positive</td>
</tr>
<tr>
<td>The aura is accompanied, or followed by headache within 60 minutes</td>
</tr>
<tr>
<td>4. Not explained by another ICHD-3 diagnosis</td>
</tr>
</tbody>
</table>

Table 2. Episodic syndromes associated with migraine

<table>
<thead>
<tr>
<th>Condition</th>
<th>Age group</th>
<th>Clinical features</th>
<th>Duration of attacks</th>
<th>Associated features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic vomiting syndrome</td>
<td>4–7 years</td>
<td>Episodic and recurrent vomiting</td>
<td>Hours to days</td>
<td>Predictable periodicity and attacks lasting for more than an hour to up to 10 days</td>
</tr>
<tr>
<td>Abdominal migraine</td>
<td>10–12 years</td>
<td>Episodic periumbilical dull abdominal pain</td>
<td>Hours to days</td>
<td>Loss of appetite, nausea, vomiting, and pallor</td>
</tr>
<tr>
<td>Benign paroxysmal vertigo</td>
<td>4–6 years</td>
<td>Sudden onset of vertigo manifesting as dizziness or ataxia</td>
<td>Minutes to hours</td>
<td>Ataxia, nystagmus, pallor, and a sense of fearfulness</td>
</tr>
<tr>
<td>Benign paroxysmal torticollis</td>
<td>Early infancy (2–5 months)</td>
<td>Recurring and episodic unilateral head tilting that happens at consistent intervals</td>
<td>Minutes to days</td>
<td>Irritability, ataxia, pallor, malaise, vomiting</td>
</tr>
<tr>
<td>Infantile colic</td>
<td>Early infancy (peaks at 6 weeks)</td>
<td>Excessive crying</td>
<td>Exceeding 3 hours daily, occurring more than 3 days weekly, persisting for a duration surpassing 3 weeks</td>
<td>No abdominal distension or vomiting</td>
</tr>
<tr>
<td>Alternating hemiplegia of childhood</td>
<td>Infancy</td>
<td>Episodes of alternating hemiplegia</td>
<td>Each episode lasts for minutes to days</td>
<td>Encephalopathy, paroxysms of dystonia, choreoathetoid movements, and autonomic dysfunction</td>
</tr>
</tbody>
</table>

Table 3. The ICHD-3 diagnostic criteria of tension-type headache and cluster headache

**Tension-type headache (infrequent)**
1. Minimum of 10 headache episodes occurring for less than 1 day per month on average (<12 day/year) and fulfilling criteria 2–4
2. Lasting from 30 minutes to 7 days
3. At least two of the following four characteristics:
   - Bilateral location
   - Pressing or tightening characteristic
   - Mild-moderate intensity
   - Not exacerbated by routine physical activity
4. Both of the following:
   - No nausea or vomiting
   - Not more than one of either photophobia or phonophobia
5. Not better explained for by other ICHD-3 diagnosis

**Cluster headache**
1. At least five attacks satisfying criteria 2–4
2. Severe to very severe unilateral orbital, supra-orbital and/or temporal pain lasting 15 minutes to 3 hours if not treated
3. One or both of the following:
   a) At least one of the following symptoms or signs, ipsilateral to the headache:
      - Conjunctival injection and/or lacrimation
      - Nasal congestion and/or rhinorrhea
      - Eyelid edema
      - Forehead and facial sweating
      - Miosis and/or ptosis
   b) A sense of restlessness or agitation
4. Headache frequency between 1 every other day and 8 per day
5. Not better explained by other ICHD-3 diagnosis


**Approach to Pediatric Headache**

1. **History and clinical examination**
   It is important to directly obtain information about headache from the child whenever possible. Older children and adolescents can provide detailed and accurate descriptions of their headaches. Parents can offer valuable insights into the child’s behavior, school performance, developmental milestones, and family history. A thorough account of a child’s behavior during acute attacks can provide insights into additional symptoms. For instance, a decreased appetite during attacks might indicate nausea, and a preference for reclining in a quiet, dark room could suggest sensitivity to light and sound.
   The primary objective of obtaining a headache history in chil-
Children is to identify red flag signs that may indicate the presence of a secondary cause of headache. An occipital headache without red flags in the history and normal findings on a neurological examination does not warrant imaging [30]. Nevertheless, the coexistence of an occipital headache with an abnormal neurological examination in children has been linked to brain tumours [31]. Features that warrant heightened concern and further evaluation are as follows [32]:

1. A new onset and worsening headache
2. Headache that awakens the child or occurs consistently upon awakening from sleep
3. Occipital headache
4. Age <6 years
5. Personality change
6. Focal neurological deficit (ataxia, weakness, diplopia)
7. Nuchal rigidity
8. Headache associated with postural variation in intensity
9. Headache intensifying with coughing or straining
10. Recurring thunderclap headaches
11. Focal neurological deficits, or an abnormal finding in a comprehensive neurological assessment (including abnormalities in an eye examination, papilledema, cerebellar signs)
12. Signs of systemic disease or known systemic disorders in children. The clinician should look for neurocutaneous stigmata, developmental delays, and explore potential neurovascular and neurogenetic conditions that could be linked to secondary headaches.

A thorough clinical examination is crucial to avoid overlooking secondary causes of headaches. This involves assessing vital signs to identify hypertension or fever. Impaired growth could indicate a chronic underlying disease, while macrocephaly might be attributed to underlying hydrocephalus. A fundus examination is necessary to rule out papilledema in relevant clinical settings, along with an assessment of visual acuity [33]. A comprehensive neurological examination is equally vital, as serious neurological conditions with secondary headaches are often associated with multiple neurological deficits on examination [31].

2. Neuroimaging
The American Academy of Neurology (AAN) and Child Neurology Society advises against imaging when the clinical history lacks associated risk factors, and the child’s examination is normal [34]. Despite these recommendations, neuroimaging in routine practice is frequently done even in the absence of red flags [35]. Whenever clinically indicated, magnetic resonance imaging is preferred over computed tomography. Contrast imaging is preferred in the setting of possible central nervous system infection. The presence of thunderclap headache necessitates additional angiography.

3. Other investigations
Routine laboratory investigations have a limited role in the evaluation of headache in absence of relevant clinical features. A CSF examination should be done if central nervous system infection is suspected or to document the opening pressure. Electroencephalography should be avoided in the assessment of episodic headaches [34].

Management of Migraine

1. Acute management
The goal of acute management is to terminate the migraine attack early, enabling a return to normal activities. General measures include avoiding environmental noise, isolating the child in a silent and dark room, and encouraging the child to go to sleep. Intravenous hydration is warranted if the child presents to emergency room [36].

Medications useful in acute treatment of migraines include analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs),...
acetaminophen, triptans, and antiemetics. The effectiveness may vary; thus, a trial of different medications may be required on an individual basis. Randomized placebo-controlled trials have demonstrated the effectiveness of both acetaminophen and ibuprofen in the acute treatment of migraines in children. A three-way crossover trial comparing acetaminophen and ibuprofen for the acute treatment of migraines in children found that paracetamol showed greater efficacy at 1 hour post-administration, whereas ibuprofen was found to be more effective overall [37]. A double-blind, placebo-controlled trial concluded that ibuprofen is effective for acute migraine treatment. A sex difference was found, with boys showing significantly higher rates of response [38]. Naproxen has been found to be effective compared to a placebo [39]. A combination of naproxen with sumatriptan has been evaluated in adolescents and was found to be both safe and effective [40]. A double-blind clinical trial investigating intravenous ketorolac and prochlorperazine reported that ketorolac was successful in 55% of children, but was inferior to prochlorperazine (85%) [41].

Triptans are agonists of serotonin receptors with an affinity for 5-hydroxytryptamine (5-HT1B/1D) receptors [42]. The U.S. Food and Drug Administration (FDA) has approved four triptans for the acute treatment of migraines in children aged 12 to 17 years: almotriptan, zolmitriptan, rizatriptan, and sumatriptan/naproxen. Triptans should be given as single dose, administered once in a 24-hour period. Although administering a second dose 2 hours after the first may be deemed safe, the effectiveness of such a regimen has not been definitively established [43]. In cases where nausea and vomiting are prominent, the early administration of an antiemetic may alleviate symptoms and promote better sleep. Commonly used antiemetics include promethazine, prochlorperazine, metoclopramide, and ondansetron. The doses of various drugs for acute management of headache in children are given in Table 5. According to a Cochrane review, ibuprofen surpasses placebo in effectiveness, while paracetamol does not show superiority over placebo. Triptans have been found to be superior to placebo and associated with minor side effects. Additionally, the combination of sumatriptan and naproxen combination has demonstrated superiority over placebo, whereas oral dihydroergotamine did not show superiority over placebo [44]. It is crucial to highlight that triptans should not be used in children with ischemic vascular disease or arrhythmias [45].

The management of migraine includes lifestyle modifications, acute treatment, and preventive treatment. Children may need a combination of these three approaches. The treatment objectives should aim at consistently and effectively minimizing symptoms with the fewest possible side effects, facilitating a prompt return to normal function [35,46]. The choice among treatment options depends on multiple factors, including the clinical context, patient values and preferences, comorbid conditions, the adverse effect profile, availability, cost, insurance coverage, and clinician familiarity with specific treatments.

Neuromodulation is not approved by the FDA or recommended by the AAN guidelines for the acute treatment of headaches in migraine. However, various non-invasive neuromodulation modalities have been tried such as transcranial magnetic stimulation (TMS), non-invasive vagal nerve stimulation, and non-invasive electrical stimulation.

An approach to management of acute migraine with summary of available modalities is given in Fig. 2.

1) **Lifestyle modifications**

A SMART plan should be considered while counseling the child and parents.

### Table 5. Drugs for acute management of migraine in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Acetaminophen</td>
<td>10–15 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>Maximum of 5 doses in a day</td>
</tr>
<tr>
<td>2 Ibuprofen</td>
<td>10 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>Maximum 400 mg per dose and maximum daily dose is 2,400 mg per day.</td>
</tr>
<tr>
<td>3 Naproxen</td>
<td>5–7 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>Maximum 1,000 mg per day</td>
</tr>
<tr>
<td>4 Ketorolac</td>
<td>Intravenous: 0.5 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>Maximum dose is 30 mg per dose. Oral: 1 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>Maximum dose 10 mg per dose and maximum daily dose 40 mg per day</td>
</tr>
<tr>
<td>5 Rizatriptan</td>
<td>Less than 40 kg: 5 mg</td>
</tr>
<tr>
<td></td>
<td>More than 40 kg: 10 mg (FDA labelled for 6 to 17 years)</td>
</tr>
<tr>
<td>6 Zolmitriptan nasal spray</td>
<td>Less than 40 kg: 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>More than 40 kg: 5 mg (FDA labelled for 12 to 17 years)</td>
</tr>
<tr>
<td>7 Sumatriptan/naproxen combo</td>
<td>Less than 40 kg: 10 mg/60 mg</td>
</tr>
<tr>
<td></td>
<td>More than 40 kg: 85 mg/500 mg (FDA labelled for 12 to 17 years)</td>
</tr>
<tr>
<td>8 Almotriptan</td>
<td>Less than 40 kg: 6.25 mg</td>
</tr>
<tr>
<td></td>
<td>More than 40 kg: 12.5 mg (FDA labelled for 12 to 17 years)</td>
</tr>
<tr>
<td>9 Promethazine</td>
<td>0.25 to 0.5 mg/kg/dose</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Maximum dose is 10 mg per dose.</td>
</tr>
<tr>
<td>10 Metoclopramide</td>
<td>0.1 to 0.15 mg/kg/dose</td>
</tr>
</tbody>
</table>

FDA, U.S. Food and Drug Administration.
S: Sleep: sufficient sleep with constant bedtimes and wake-up times on weekdays and weekends.
M: Meals: avoid fasting or skipping meals
A: Adequate hydration: increasing water intake
R: Regular exercise: aerobic exercise 30-40 minutes three times a week
T: Avoid triggers

The counseling should consist of advice on sleep hygiene, adequate hydration, regular food intake, and exercise. It is crucial to determine whether insufficient sleep, dehydration, or skipping meals are triggers. The American Academy of Sleep Medicine has issued a consensus statement outlining the recommended sleep duration for children and adolescents, taking into account their respective ages [47]. For optimal health, adolescents need a minimum of 8 hours of sleep at night. However, due to their physiologically delayed sleep phase and the fact that high schools often start earlier than would be ideal for their waking hours, adolescents frequently face challenges in obtaining the recommended amount of sleep [48]. This often leads to changes in bedtimes and wake times between weekdays and weekends, as children and adolescents try to compensate for lost sleep by sleeping on weekends.

Excessive screen time may be linked to primary headaches in children, and it is important to reduce the time spent on screens [49]. Studies in the adult population have suggested a correlation between decreased physical activity and a heightened prevalence of migraines. Furthermore, a study found that participating in 40 minutes of aerobic exercise three times a week yielded results comparable to using topiramate for the preventive treatment of migraines in adults [50,51]. It is essential to consider other risk factors for headaches in children, including potential stressors, such as instances of physical or emotional abuse, as well as incidents of bullying [52]. Children with migraines often report comorbidities including anxiety and mood disorders. It is crucial to address these additional health concerns as they have been identified as potential factors that can impact both headaches and overall quality of life [53].

2) Behavioral interventions
Cognitive behavioral therapy (CBT) is an evidence-based modality for pediatric migraines. It provides coping mechanisms to effectively deal with pain and assists in modifying factors that precipitate headaches. The components of CBT include psychoeducation (information about the prevalence and nature of the disease), self-monitoring, coping skills, parent training and relapse prevention [54]. A systematic review and meta-analysis of 14 studies found that the odds ratio for a 50% or greater reduction in headache activity after at least 3 months of CBT was 9.18 (95% confidence interval, 5.69 to 14.81; P<0.001) [55].

3) Pharmacological management
The focus should be on identifying the treatment that provides maximum benefits with minimum side effects. Children and parents should be counselled on monitoring possible adverse effects. To minimize these effects, medications should be initiated at the lowest effective dose and then incrementally adjusted to attain the desired target dose. Preventive pharmacological treatment is indicated when headaches are frequent, prolonged, or disabling. Additionally, preventive therapy is employed when patients fail to respond to or are intolerant of acute treatment. The preventive medications discussed here are confined to those that have been studied specifically in children. Possibly useful oral agents include cyproheptadine, propranolol, amitriptyline, topiramate, cinnarizine, and flunarizine. Injectable agents include CGRP antagonists and botulinum toxin. In addition, non-invasive neurostimulation is a promising modality for preventing migraine in children.

Fig. 2. Approach to the management of acute migraine attacks. NSAID, non-steroidal anti-inflammatory drug.
(1) Topiramate
The FDA has approved the use of topiramate in migraine prevention among children aged 12 to 17 years old. In a quasi-experimental study, topiramate resulted in significant reduction in disability associated with migraine [56]. However, a three-arm trial spanning 24 weeks reported no difference in the reduction of either headache frequency or disability among children and adolescents with migraines when treated with amitriptyline, topiramate, or a placebo [57]. The common side effects of topiramate include cognitive slowing, paresthesia, and weight loss. Other potentially serious side effects include renal stones, glaucoma, and teratogenicity.

(2) Sodium valproate
There have been no placebo-controlled trials conducted for valproate in the prevention of migraines in children. A randomized trial identified no discernible difference between valproate and propranolol in terms of their effectiveness in preventing migraines [58]. The side effects of valproate encompasses alopecia, tremor, teratogenicity, hepatotoxicity, pancreatitis, leukopenia, and thrombocytopenia.

(3) Amitriptyline
The Childhood and Adolescent Migraine Prevention (CHAMP) trial reported no benefit of amitriptyline over placebo and topiramate [57]. Significant side effects of tricyclic antidepressants such as amitriptyline are dry mouth, constipation, sedation, an increase in appetite, weight gain, occasional orthostatic hypotension, and cardiotoxicity [59].

(4) Propranolol
Studies on the use of propranolol for preventing pediatric migraines have produced mixed results. When low-dose propranolol was compared with amitriptyline, both were found to be equally effective in reducing the number of migraine attacks in children, with propranolol demonstrating fewer side effects [60]. A trial concluded that, at both the 4- and 8-week post-treatment marks, propranolol was found to be less effective than pregabalin in preventing migraines [61]. Propranolol may lead to side effects such as fatigue, sleep disturbance, and light-headedness.

(5) Cinnarizine
Cinnarizine, which exerts dual functions as an antihistamine and a calcium channel blocker, appears to be effective in migraine prevention. In a placebo-controlled trial involving children aged 5 to 17 with migraines, the cinnarizine group demonstrated a more than 50% reduction in headache frequency as compared to the placebo. Potential side effects of cinnarizine may include mild drowsiness and, less commonly, weight gain [62].

(6) Flunarizine
Observational studies have reported the efficacy of flunarizine, revealing that over half of those treated experienced a headache frequency reduction of more than 50% [63]. The AAN/American Headache Society guidelines concluded that there is insufficient evidence to ascertain whether flunarizine is more effective than a placebo in reducing migraine attacks in children [64]. Nevertheless, a systematic review and meta-analysis conducted in 2019, which included studies involving both adults and children, concluded that flunarizine demonstrated modest effectiveness in reducing headache frequency compared to a placebo and appeared to be effective in children [65]. Weight gain and sedation are the most frequent adverse effects of flunarizine.

(7) Botulinum toxin
The effectiveness of botulinum toxin injections in children is currently uncertain. Trials in adults have produced conflicting results regarding the efficacy of onabotulinumtoxin-A (BoNTA) injections in reducing the frequency of headaches in chronic migraine [66–67]. A systematic review of seven studies showed only modest reductions in headache frequency, duration, and intensity among responders [68]. BoNTA is administered every 3 months via intramuscular injection. The most common adverse effects observed in treated groups are neck pain and musculoskeletal pain [66]. A retrospective study in children and adolescents found that BoNTA injections significantly reduced headache severity and frequency [69]. BoNTA is currently not approved for adolescents <18 years of age.

(8) CGRP antagonists
CGRP is associated with the transmission of painful stimuli, as it is found in unmyelinated sensory nerve fibres. In adults, studies have shown that monoclonal antibodies to CGRP or its receptor are efficacious for migraine prevention. These antibodies are typically administered as a once-per-month self-injection. However, it is important to note that CGRP antagonists are not approved for patients under the age of 18.

4) Non-pharmacological modalities
(1) Transcranial magnetic stimulation
The FDA in the United States has approved a device designed for the acute treatment and prevention of migraines in adolescents (aged 12 years and above) and adults [70]. This device delivers brief-duration, rapidly alternating, or pulsed magnetic fields directed towards specific regions of the brain to induce electric currents.
It operates on the principle of single-pulse TMS. A pilot study found TMS to be safe in adolescents aged 12 to 17 years for migraine prevention [71].

(2) Transcutaneous nerve stimulation
Transcutaneous nerve stimulation (TNS) has shown promising results in adult population. A meta-analysis concluded that TNS is effective and well-tolerated but needs more randomized trials [72]. Nevertheless, it is important to highlight that there is currently a lack of robust evidence supporting the effectiveness of this intervention in children.

Management of Tension-Type Headache and Cluster Headache

The management of tension-type headache in pediatric patients lacks clear guidelines. Pharmacological prevention is not deemed necessary for all patients, and non-pharmacological approaches such as physical exercise, behavioral therapy, or psychological counseling may be helpful [73]. The acute attack may be terminated using NSAID or non-NSAID analgesics. There is a lack of randomized trials and commonly used preventive medications are amitriptyline, gabapentin, and topiramate.

The management of cluster-type headaches in children is also devoid of evidence-based recommendations. A systematic review of case reports has determined that oxygen inhalation, sumatriptan nasal spray, and ergotamine derivatives are the most effective treatments for acute attacks. Additionally, verapamil, gabapentin, indomethacin, and valproate have been identified as effective options for preventing these headaches [9].

Conclusion

Pediatric headache is a prevalent condition in children, leading to substantial morbidity and frequent healthcare visits. The primary culprits are often primary headaches and acute viral infections. The initial assessment is essential for identifying potential warning signs, excluding secondary or life-threatening causes of headaches, and minimizing unnecessary investigations. Migraine is the most significant and common type of headache in children and adolescents. Prompt acute management of migraines involves supportive care and analgesics, but there is a lack of clear evidence-based recommendations for preventive therapy in children, highlighting a need for further research in this area. Newer modalities including non-invasive neuro-simulation botulinum toxin and CGRP antagonists are promising and emerging therapies.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contribution

Conceptualization: AW, AKM, and SP. Methodology: AW and AKM. Visualization: AKM and SP. Writing - original draft: AW, AKM, PKC, and RS. Writing - review & editing: AW, AKM, PKC, SP, and RS.

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https://doi.org/10.26815/acn.2024.00521


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