



# Migraines in childhood as a cause of headache in adulthood – how to prevent it? A literature review

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## Abstract

**Introduction and Objective.** Migraine is the most common acute and recurrent headache in children. The pain is the result of stimulation of meningeal nociceptors. There may be a genetic predisposition to generalized neuronal hyperexcitability. Aura is caused by the cortical spreading depression (CSD). Migraines hamper daily functioning and cause adverse effects in future adult life. This review aims to introduce the most common forms and present their diagnosis and treatment methods.

**Review Methods.** The following electronic databases were searched: Pubmed, Google Scholar using the keywords ‘childhood migraine disorder’, ‘paediatric migraine’, ‘migraine in children’. Articles in English were included.

**Brief description of the state of knowledge.** The review shows both the diagnostic modalities of migraines and the latest methods of treating and preventing migraines from developing.

**Summary.** In the diagnosis of migraine in paediatric patients, particular importance is attached to a thorough clinical history. Paediatric patients suffering from migraine have a reduced density of grey matter in the frontal cortex. In the therapeutic process a multi-media approach, including lifestyle changes, psychoeducation and psychotherapy and pharmacotherapy, are important.

**Conclusions.** There is a good response to OCT analgesics in children and adolescents. There are reports in the literature that migraine occurring in children becomes a risk factor for migraines in adults. Migraines in children represent a difficult disease entity, both diagnostically and therapeutically. To-date, no significant changes have been demonstrated on imaging studies in children and the symptoms themselves may be uncharacteristic. Further research is needed to consider and implement the use of new drugs.

## Key words

childhood migraine disorder, paediatric migraine, migraine in children

## INTRODUCTION AND OBJECTIVE

Migraine is a neurobiological headache disorder caused by increased CNS excitability [1]. About 8% of children and adolescents are prone to migraine from at least the age of three months and persist throughout life. Migraine is classified as a primary headache of which there are 2 main types: with or without aura [2, 3]. Chronic migraine affects between 1% – 2% of the global population, and is the most common primary headache in children and adolescents. Recurrent headaches due to migraine occur in about 1 in 10 children. In addition, up to 18% of patients presenting to the paediatric emergency room are associated with migraine [4, 5]. In children under the age of 7 years, the prevalence of primary headaches, particularly migraine, is up to 4% of the general population. However, an underestimation of the actual prevalence must be taken into account, due in part to the lack of specific diagnostic markers, as well as the difficulty children have in describing the nature of their pain [6]. The

incidence of migraine increases with age. Before puberty, it is higher in males than in females, while in puberty and post-puberty the proportions change and migraine is much more common in females than in males [7].

Headaches, especially migraines, significantly reduce quality of life. Young patients with the disorder are more likely to perform worse academically compared to children without headaches, and are more likely to miss school than children with episodic tension headache [8, 9]. Despite this, current complaints are still sometimes underestimated by parents, which is why it is important to make a proper, unequivocal diagnosis in a child in time to prevent reduced intellectual performance, reduced quality of life, and unnecessary pain. Interacting psychological, biological and environmental factors contribute to the development of migraine, but considering only these factors without analyzing the history, sensitivities and experiences of an individual child can make it difficult to understand the complexity of the problem that is migraine [10].

Reduced leisure time, pressure from school, family, and peer group appear to be important external factors influencing the onset of migraine. Family conflicts, bullying, child abuse, and other factors related to emotional stress

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are also relevant. On the other hand, individual factors that predispose to migraine include being overweight, smoking, reduced physical activity, and increased alcohol and caffeine consumption [10, 11].

Periodic paediatric syndromes, or paediatric migraine variants or migraine precursors, are periodic or paroxysmal disorders that occur in patients with migraine with or without aura, or in such patients who are at increased risk of migraine [12]. They represent early expression of genes responsible for migraine – over time they become apparent in the form of migraine headaches. These include benign paroxysmal torticollis, benign paroxysmal vertigo, abdominal migraine, and cyclic vomiting syndrome – knowing these can prevent delaying a migraine diagnosis and help direct appropriate therapy [13].

The aim of this review is to highlight the diagnostic and complex therapeutic difficulties presented by migraines in children, as well as the need for a multifaceted approach to the patient [11] and present whether current comorbidities in children have an impact on the occurrence of migraines.

## MATERIALS AND METHOD

The following electronic databases were searched: Pubmed, Google Scholar using the key words ‘childhood migraine disorder’, ‘paediatric migraine’, and ‘migraine in children’. Articles in English were included. Exclusion criteria were abstracts and the time of publication – studies more than 8 years old were rejected. In the end, 68 articles met the criteria and were selected.

**Pathophysiology.** Migraine headache is the result of stimulation of meningeal nociceptors, and in many cases, develops secondary to the activation of brain regions that are responsible for the neurological symptoms present during the aura and prodrome. Meningeal nociceptors originate from the trigeminal-vascular system (a system of neurons that include branches of the trigeminal nerve and innervate the cerebral blood vessels). Stimulation of the trigeminal vascular pathway is one of the pathomechanisms responsible for photophobia and skin allodynia during migraine [13]. There is no data explaining how prodromal symptoms are associated with the stimulation of the afore-mentioned nociceptors. Ferrari et al. conducted studies in animal models which suggested that in the case of migraine, there may be a genetic predisposition to generalized neuronal hyperexcitability [14, 15].

A study by Maniyar et al. showed that such areas of the brain as the hypothalamus, midbrain, periaqueductal gray matter and dorsal part of the pons, as well as the occipital, temporal and prefrontal cortex are involved in the occurrence of prodromal symptoms [16]. Due to the role of the hypothalamus, and especially orexin produced by it, which is regulation of sleep, temperature and neuroendocrine and nociceptive processes, it is likely that its activation is responsible for prodromes in the form of sleep or eating disorders, and consequently cause migraine headache [17].

There are two theories that, if proven, could enable work on a therapy that, when applied in the prodromal phase, would prevent the development of the pain phase of migraine. The first of theory suggests that psychological and emotional stimuli influence the parasympathetic and sympathetic tone of

the meninges, towards the predominance of parasympathetic tone and thus activate the meningeal nociceptors [18, 19]. The second possibility involves lowering the threshold for transmission of nociceptive trigeminal vascular signals from the thalamus to the cerebral cortex through hypothalamic and brainstem neurons that respond to physiological and emotional changes in the body [13, 20]. This would explain why migraine triggers include strong odours, specific foods, hunger, sleep deprivation, and stressful situations [21].

Studies showed that within the trigeminal ganglion, the majority of nerve cells contain CGRP (calcitonin gene-related peptide receptor) and CGRP-positive fibres which surround the blood vessels in both the cranial and non-cranial areas [22, 23]. CGRP functions as a potent dilator of cerebral arteries and arterioles by activating adenylyl cyclase in the muscle cells [24, 25]. Studies have shown the ability of CGRP to specifically relax cortical arterioles without affecting venules. Interestingly, disrupting the sensory nerves containing CGRP did not impact the baseline blood flow or its control mechanisms [25, 26]. Instead, CGRP seems pivotal in a protective reflex, known as the trigeminovascular reflex, in which it responds to the local narrowing of cerebral blood vessels by causing dilation and maintaining adequate blood flow [27, 28, 29]. These findings strongly implicate CGRP in the development of migraines. Further studies confirmed the selective release of CGRP from the trigeminal system during spontaneous migraine attacks, and this release could be hindered by medications designed to treat migraines, e.g. triptans [30].

The mechanism of migraine aura formation is better understood. Studies suggest that cortical spreading depression (CSD) – a slow-spreading wave of depolarization/excitation followed by hyperpolarization/inhibition in cortical and glial neurons – is responsible for this [31].

Migraine with aura in children may present as the ‘Alice in Wonderland Syndrome’ (AIWS), first described in 1952 by Lippman, which consists of transient episodes of visual hallucinations and perceptual distortions in which objects or parts of the body are perceived to have changed in various ways (metamorphopsia), including enlargement (macropsia) or reduction (micropsia) [21]. Other symptoms seen in AIWS include kinetopsia, auditory hallucinations and verbal illusions, hyperacusia/hearing loss, dyschromatopsia, zoopsia, and complex visual hallucinations.

Studies have shown that the main areas of the brain where activation changes occur during an AIWS episode are the temporo-occipital, parieto-occipital and temporo-parietal junctions (TOJ, POJ and TPJ). Depending on the symptoms experienced by the patient, they are either hypo- or hyper-activated [31]. Other parts of the brain where changes have been observed in single-photon emission computed tomography (SPECT) are the frontal and parietal lobes, and the corpus callosum [32, 33].

## PERIODIC SYMPTOMS AND SYNDROMES

**Periodic childhood symptoms.** The classic migraine attack can be divided into a prodromal phase, aura, headache and postdromal phase, but it is not necessary that all phases occur in a given patient or in a given attack [34].

The prodromal phase occurs up to 48 h before the onset of pain symptoms or aura [34]. In a study by Cuvelier et al.

based on telephone interviews with paediatric patients and their caregivers, a single symptom was reported by more than 60% of participants, and more than half reported two or more [35]. The most frequently reported symptoms were facial changes, fatigue and irritability. Of the other symptoms, feelings of anxiety/stress, phonophobia, increased yawning, photophobia, and a few per cent cacosmia, sleep disturbance, hyperactivity, increased appetite, sadness, neck stiffness or neck pain and nausea were also common [34, 35]. Karsen et al. cited fatigue, neck stiffness and yawning as the most common, and also mentioned dizziness, polyuria, visual disturbances, increased thirst and pale skin. Two or more symptoms were reported by 85% of the subjects [36].

The aura phase in children occurs in 10–20% of cases, and the prevalence is positively correlated with age. Aura symptoms usually develop within 5–20 min and resolve within 60 min [37, 38]. Aurae may precede or overlap with the headache phase. In paediatric patients, the most common form is visual aura, with the main reported symptoms in a study by Petrusic et al. on a population of adolescents, were sparkling gloom, blurred vision, tunnel vision and zigzag lines [37]. Colour dysdiagnosis or image distortion was also common, described in the literature as ‘Alice in Wonderland Syndrome’ (AIWS) [39].

The second most common type of aura in children and adolescents is somatosensory aura [37, 40], usually manifested by a feeling of numbness. In studies, it most commonly involved the left upper limb, followed by the mouth and/or face, tongue and lower limbs with the presentation of a ‘marching’ gait [37].

During the aura phase, symptoms that are higher cortical centre dysfunctions (HCD) are also frequently observed, mainly taking the form of slowed speech and other dysphasic disorders, *déjà vu* phenomenon, dyslexia and/or dyscalculia. Memory disturbances (including retrograde amnesia), disorientation in space and impaired gnosis may also occur [37, 40].

Truncal aura is a distinct variant of migraine (migraine with truncal aura, basilar migraine, basilar artery migraine). Symptoms originate in areas of the brain supplied by the basilar artery or the posterior cranial fossa and include visual disturbances, dizziness, cranial nerve damage, ataxia, dysarthria, paraesthesia, paresis, transient disturbance of consciousness and tinnitus. The headache is more often localised to the occipital region than in other types of migraine in children [40].

The types of aura may overlap taking a complex form or change between attacks [34, 37].

A headache attack in children lasts from 2 – 72h and is usually less severe than in adults. The location of the pain is usually bilateral in the frontotemporal region and the character is pulsatile. The pain is accompanied by nausea or vomiting, photophobia and phonophobia, which are often described as more persistent than the pain itself [34, 41]. Pre-school children during an episode are described by their parents as pale, lethargic and often complain of abdominal pain and fatigue. The pain and associated symptoms can be a difficult experience for pre-school children to define and manifest as changes in behaviour. They often seek dark spaces to sleep, rock and complain of abdominal pain [8]. Older adolescents are more likely to have unilateral headaches, and the location of the pain may change during the seizure [8].

Trigeminal-autonomic symptoms in the paediatric population are more common in patients with migraine than in patients with other primary pain. The most common symptoms are lacrimation, conjunctival redness, a feeling of fullness in the ears, nasal leakage, swelling of the eyelids, facial redness and orbital swelling [34].

The postdromal phase occurs after the pain has subsided. In a study in a paediatric population, symptoms started within 30 min after pain resolution and resolved by 3 h [42, 43]. The phase occurred more frequently in patients with aura, and the most commonly reported symptoms included asthenia, cognitive impairment, pallor, anorexia, lethargy and nausea [34]. In a study by Mamouri et al., thirst, lethargy and visual disturbances were among the symptoms most commonly reported [43].

Chronic migraine is characterised by a headache for at least 15 days per month, over a period of 3 consecutive months, without concomitant organic pathology, which shows features of migraine pain for at least 8 days per month [41]. Children with chronic migraine usually experience at least 2 types of headache. One as severe intermittent headaches, resembling a classic migraine attack with associated symptoms, and a frequency specific to the patient. In addition to these severe attacks of pain, there is an almost daily continuous headache whose intensity varies throughout the day. Its nature is similar to episodes of severe pain, but much less intense or resembling tension pain. In chronic headache, symptoms such as sleep difficulties dizziness, anxiety and lowered mood, muscle pain and gastrointestinal distress often co-occur, contributing to a significant limitation of daily activity [8].

**Periodic childhood syndromes.** In the third edition of the International Classification of Headache Disorders (ICHD-3), abdominal migraine, cyclic vomiting syndrome, benign paroxysmal dizziness and benign paroxysmal torticollis are presented as periodic syndromes that may be precursors of migraine [41]. A characteristic feature of the above disorders is their episodic, reversible and patterned nature. Patients do not present with any pathological symptoms between attacks. Children with intermittent syndromes usually have a positive family history of migraine and there is a marked tendency for them to develop into attacks of typical migraine as the child matures [34–36].

**Abdominal migraine.** Characterised by paroxysmal abdominal pain in a periumbilical, medial or hard-to-define location, of moderate to severe intensity, lasting from 2–72 h, untreated or treated ineffectively. The pain has an acute onset and is accompanied by pallor, anorexia, or vomiting [4, 44]. The first attacks of abdominal migraine usually occur in early childhood and the most common triggers are psychological stress and physical exhaustion [4, 45].

**Cyclic vomiting syndrome (CVS).** The main complaint is episodes of persistent vomiting lasting between 1 h and 10 days. Characteristic features include the onset of the episode early in the morning, a stereotypical seizure pattern for the patient and intervals between episodes without complaints [8]. Nausea and vomiting occur every 5–10 min, and at least 4 per hour are required to meet ICHD-3 criteria [41]. Seizures usually begin in early childhood and resolve with the onset of classic migraine headache attacks, and less commonly persist into adulthood.

**Benign paroxysmal positional vertigo (BPV).** Dizziness occurs suddenly, without a discernible cause, and lasts from a few seconds to a few minutes. They may be accompanied by nystagmus, ataxia, nausea or vomiting, pallor and fearfulness [41, 44]. No neurological or audiometric abnormalities or vestibular dysfunction are found between seizures. They most commonly begin between 2–5 yrs of age [44].

**Benign paroxysmal torticollis.** This syndrome begins in infancy, around 5–6 month [44, 45], and resolves completely usually between 3–4 years of age [44]. Episodes of torticollis usually last a few hours, but can last up to several days, and resolve spontaneously. They occur at regular intervals and are not preceded by warning symptoms [44, 45].

**Diseases associated with migraine.** Migraine headaches in children make it very difficult for them to function on a daily basis. Decreased mood and reduced bonding in peer relationships can also be found [46].

**Coeliac disease.** A study by L. Sabino et al. found that children with coeliac disease had a significantly higher incidence of migraine headaches (24% of patients) compared to the control group (8%). It was concluded that this may be due to an immunological imbalance with a predominance of pro-inflammatory cytokines, with a lack of regulation of vascular tone. Patients were additionally found to be deficient in elements and vitamins, including magnesium, which is responsible for tension. The children were therefore treated with gluten-free products. In all subjects, there was an improvement or complete resolution of symptoms after the introduction of these supplements into the diet. Another study on a smaller population of 7 children confirmed that among 5 of them there was a complete cessation of migraine headaches after the gluten-free diet, while 2 had a significant decrease in symptoms. It was speculated that cerebral hypoperfusion and perivascular inflammation may significantly affect the headaches. Further research is needed to understand their exact pathophysiology and relationship between the presence of coeliac disease [46].

**Endometriosis.** An association between the co-occurrence of migraines and endometriosis has been demonstrated. A study by J. Miller et al. on a group of 296 adolescents, 205 of whom had both diseases, 91 with endometriosis alone and the rest with neither disease. The mean age was 17.4 years and the patients had normal BMI. The study found that adolescent girls with endometriosis were more likely to report migraine headaches (69.3%) compared to the other subjects. Female participants whose first menstrual period occurred after the age of 14 were almost 70% less likely to have migraines. The study confirmed a linear relationship between the presence of endometriosis and worsening migraine headache.

A clinical study conducted by Yang et al. on a group of 20,220 participants with endometriosis and migraine showed that migraines were almost 1.7 times more frequent in women struggling with endometriosis than in those not suffering from it. In addition, these patients show greater sensitivity to pain, especially in the pelvic area. The risk of endometriosis with the most severe migraine pain is almost twice as high as in patients who do not complain of headaches. In addition, patients whose first menstrual period occurs before the age of 14 who have endometriosis are at increased risk of migraines.

Adolescent girls should be monitored very closely to reduce the risk of these two comorbidities [47].

**Sleep problems.** Children complaining of migraine headaches also have serious sleep problems. A study conducted by Suzy M. Walter on a group of 648 children found that around 50% of migraine sufferers additionally suffer from obstructive sleep apnoea. This problem leads to the development of numerous cardiovascular diseases, problems at school or neuropsychiatric disorders. In addition, the study found that 34% of children are affected by anxiety or depression. These reports suggest that it is extremely important to monitor a child's current state of health. Any headache that lasts for a prolonged period of time or changes in nature should be diagnosed and treated as soon as possible, as a trivialised problem can lead to serious health consequences later in life [48].

## DIAGNOSTICS

In the diagnosis of migraine in paediatric patients (Tab. 1), particular importance is attached to a thorough clinical history. It is precisely the detailed question about the location, nature of pain, duration of symptoms, accompanying symptoms or factors that aggravate the pain that may direct the attending physician to make an accurate diagnosis. An important role in completing the interview is also played by parents, who are often able to notice more symptoms of the disease in their child.

The next step in the diagnosis of headache in children is a physical examination, including a neurological examination. Despite the difficulties that it often causes, especially in contact with smaller children, it should not be overlooked. It is important to carefully assess the awareness, cognitive functions and psychomotor skills of the young patient, and to take into account the fact that some symptoms may change over time and several follow-up visits are needed to ensure that nothing is missed.

Accurate differential diagnosis allows the separation of childhood migraines from other causes of primary and secondary headaches, including conditions that may be life-threatening to the child, such as meningitis. Among the symptoms that arouse concern for a parent or clinician, can be distinguished: headache on awakening from sleep, vomiting in the morning, mood swings with personality changes, or pain occurring after a head injury. These are the so-called 'red flags' that should not be missed at any stage of diagnostics [49, 50].

The use of electroencephalography in the diagnosis of migraine or migraine with aura is limited to rare cases of migraine headaches associated with epilepsy. EEG allows examination of the temporal relationship between the migraine aura and the occurrence of an epileptic seizure, and to distinguish the migraine aura from the symptoms of occipital epilepsy. Alpha wave activity was also demonstrated under visual stimulation in patients with migraine with aura, while de-synchronization of the basal alpha wave rhythm was observed in a control group [51].

To-date, few cases of the use of magnetic resonance imaging in the diagnosis of migraine in children have been described in the literature. Studies have shown that paediatric patients suffering from migraine have a reduced density of grey

**Table 1.** ICHD-3 Diagnostic Criteria for episodic syndromes that may be associated with migraine [28]

<b>Abdominal migraine</b>					
A	B	C	D	E	F
At least 5 attacks of abdominal pain, fulfilling criteria B–D	Pain has at least 2 of the following 3 characteristics: 1. midline location, periumbilical or poorly localized 2. dull or 'just sore' quality 3. moderate or severe intensity	During attacks, at least 2 of the following: 1. anorexia 2. nausea 3. vomiting 4. pallor	Attacks last 2-72 hours when untreated or unsuccessfully treat	Complete freedom from symptoms between attacks	Not attributed to another disorder.
<b>Cyclic vomiting syndrome</b>					
A	B	C	D	E	
At least 5 attacks of intense nausea and vomiting, fulfilling criteria B and C	Stereotypical in the individual patient and recurring with predictable periodicity	All of the following: 1. nausea and vomiting occur at least 4 times per hour 2. attacks last $\geq 1$ hour and up to 10 days 3. attacks occur $\geq 1$ week apart	Complete freedom from symptoms between attacks		
<b>Benign paroxysmal torticollis</b>					
A	B	C	D	E	
Recurrent attacks in young child, fulfilling criteria B and C	Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days	At least 1 of the following associated symptoms or signs: 1. Pallor 2. Irritability 3. Malaise 4. vomiting 5. ataxia	Normal neurological examination between attacks	Not attributed to another disorder	
<b>Benign Paroxysmal Vertigo</b>					
A	B	C	D	E	
At least 5 attacks fulfilling criteria B and C	Vertigo occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness	At least 1 of the following associated symptoms or signs: 1. Nystagmus 2. Ataxia 3. Vomiting 4. Pallor 5. Fearfulness	Normal neurological examination and audiometric and vestibular functions between attacks		

matter in the frontal cortex, which may result in cognitive impairment in the future. In addition, it has been observed that the temporal or fusiform gyrus is enlarged in the child's brain. This symptom is absent in adults with migraine and is probably the cause of the different course of migraine in these two age categories. Further studies on the use of magnetic resonance imaging in the diagnosis of headache in a paediatric patient may bring closer the pathomechanism of migraines and contribute to more effective treatment [52].

## TREATMENT

In the therapeutic process of migraine in children, a multi-media approach including lifestyle changes, psychoeducation and psychotherapy and pharmacotherapy is important [53].

**Basic treatment of migraine.** Education of patients and their families about the management of migraine attacks plays a major role in the therapeutic process. It is important to instruct families and patients on the need to interrupt the pain attack as early as possible with medication and to ensure access to it both at home and outside the home [54, 55]. Lifestyle modification is important, especially ensuring adequate quantity and quality of sleep, identifying triggers for the attack and ensuring proper hydration, a balanced diet and regular meals, avoidance of caffeine, and regular moderate physical activity [56].

Seizure management should be tailored to the type of migraine, the nature of the pain, the age of the patient and take into account comorbidities. The aim is rapid and complete resolution of pain with minimal side-effects [54]. There is a good response to OCT analgesics in children and adolescents.

The most commonly used in the paediatric population is ibuprofen (10 mg/kg). In children with contraindications to the use of NSAIDs (e.g. allergic reactions), paracetamol (10–15 mg/kg) is suggested [56].

When treatment of seizures with OCT analgesics is ineffective, triptans (5HT<sub>1B/1D</sub> agonists) are recommended. FDA-approved for use in the paediatric population in children over 12 years of age are zolmitriptan NS (5mg), sumatriptan NS (20mg) and almotriptan OT (6.25 or 12.5 mg), and in children over 6 years of age, rizatriptan ODT (5 or 10 mg) [54].

**Acute migraine attack.** In an acute migraine attack, with insufficient response to *ad hoc* home medication, it may be necessary to initiate intravenous treatment. In children, a combination of dopamine agonists with intravenous saline solution, ketorolac and/or intravenous DHA is particularly effective. The most commonly used dopamine agonists are metoclopramide and prochlorperazine [56, 57].

Treatment should also address concomitant symptoms – nausea, vomiting, photophobia, and phonophobia. A positive response in terms of reduced photophobia and phonophobia has been observed with zolmitriptan NS and a sumatriptan/naproxen combination. For children and adolescents with severe nausea and vomiting, anti-emetics also used for other conditions – prochlorpromazine, promethazine, dimenhydrinate and metoclopramide – are recommended in cases of vomiting in the paediatric population [54].

**Chronic migraine.** In most cases, *ad hoc* treatment of seizures together with lifestyle changes is sufficient and no additional pharmacological prophylaxis is required. Initiation of treatment is suggested in patients with 3–4 seizures per month, when *ad hoc* treatment does not bring sufficient improvement and/or is poorly tolerated, and when the headache impairs the child's functioning and significantly reduces quality of life [56, 57]. Based on the American Migraine Prevalence and Prevention (AMPP) study, it is recommended that pharmacological prophylaxis should begin after the age of 12 years. The aim of prophylactic treatment is to reduce the frequency of migraine attacks and the associated disability [54].

**FDA-approved preparation.** The only FDA-approved preparation for use in children and adolescents (12–17 years) for prophylaxis is topiramate. However, studies to date show a slight advantage of topiramate over placebo in paediatric patients [54]. The use of amitriptyline, which belongs to the TMPD group and is widely used in adults, in a randomised trial in children and adolescents did not produce sufficient evidence to support a greater benefit of its use over placebo [54, 57]. In a study by Powers et al. on patients with chronic migraine in the age group 10–17 years, comparing the use of amitriptyline with concurrent behavioural therapy (CBT) and the use of amitriptyline in combination with headache education, the superiority of the combination of amitriptyline and CBT was demonstrated – reduction in seizure frequency by at least 50% and headache-related disability). However, a large response to placebo was also demonstrated (30–61% of subjects) [58]. The FDA's warning regarding the increased risk of suicidal thoughts and behaviour in patients using amitriptyline should also be borne in mind. There is also

evidence of the efficacy of cinnarizine (a calcium channel blocker) relative to placebo in preventing migraine attacks in children [59]. Studies have also shown the efficacy of the beta-blocker propranolol in reducing seizure frequency relative to placebo [54].

**Nutraceuticals.** Nutraceuticals also have a place in the prevention of migraine attacks in children, which are well tolerated by patients and have few side effects. The most commonly used are magnesium, riboflavin, coenzyme Q10 and polyunsaturated fatty acids such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and tocopherol. However, the efficacy of nutraceuticals in migraine in children and adolescents is not clearly supported by clinical trials – the results of nutraceutical trials were similar to placebo trials [56, 60]. Papetti et al. obtained positive results regarding the efficacy of palmitoyl ethanolamide (PEA) in an open-label paediatric study [61].

**Gepants.** Gepants are medications designed to address migraines, functioning as antagonists to the calcitonin gene-related peptide (CGRP) receptor. Their mechanism involves the blockade of the CGRP receptor, effectively impeding the impact of CGRP, a neuropeptide strongly linked to migraine development [62]. Clinical research has substantiated the efficacy of gepants in both treating acute migraine episodes and preventing their recurrence [63]. Notably, trials evaluating medications like rimegepant and ubrogepant have revealed considerable enhancements in pain alleviation and relief from migraine-related symptoms when compared to a placebo, accompanied by favourable safety profiles. These drugs present a viable alternative for managing migraines, particularly for individuals who exhibit poor responsiveness to or cannot undergo other treatments [64, 65]. Nonetheless, ongoing research endeavours to delve deeper into their prolonged safety, efficacy, and their position within the broader spectrum of available migraine therapies.

**Anti-CGRP monoclonal antibodies.** Are used in the prevention of episodic and chronic migraines in adults. Phase III studies of their use in the paediatric population aged 6–17 years such as OASIS (erenumab) and REBUILD (galkenezumab) are currently ongoing [66, 67]. Orders for the use of anti-CGRP monoclonal antibodies in children and adolescents developed by Szperk et al. for off-label indications, suggest considering the administration of a mAb to paediatric patients with headache 8 days per month, disability grade (PedMIDAS) 30, failure of 2 or more prophylactic therapies (pharmacological, nutraceutical and/or non-pharmacological) who are post-pubertal or, in selected cases, pre-adolescent [66].

**Non-pharmacological treatments of migraine.** In the absence of sufficient evidence for the efficacy of pharmacological therapy in reducing the frequency of migraine attacks, research into the use of non-pharmacological approaches has been undertaken. Esparhm et al. conducted a study on an age group of 12–17 years regarding the use of electrical neuromodulation – REN [68]. They observed both an alleviation of headache intensity and an improvement in quality of life functioning and a reduction in medication use, with a small number of mild side-effects [60, 68].

The potential benefits of a ketogenic diet (KD) and D-beta-

hydroxybutyrate supplementation in reducing migraine attacks are also highlighted [56, 61, 69]. However, little research has been conducted on the paediatric population to objectively confirm the hypotheses [69]. Due to the noted association between migraine and obesity in the paediatric population [70,71], weight reduction in patients with a high BMI is suggested [70].

## DISCUSSION

Migraine in children is a very complex problem that requires further research, including the search for the causes of the symptoms of this disease and new therapeutic options, especially aimed at preventing the occurrence of subsequent episodes.

The appearance of migraine in childhood usually results in the existence of this disease also in adulthood [66]. The symptoms of migraine in children are similar to those in adults although there are several differences between them: migraine attacks in children have a shorter duration, and bilateral pain appears relatively more often in young patients than in adults; instead of the pain phase there may be vomiting, nausea, abdominal pain, photophobia, sound-phobia, behaviours associated with very strong emotions – tantrums, crying, etc. – and changes in eating and sleeping behaviour [67].

Marchese et al. conducted a study on a group of people diagnosed with migraine in early childhood. 75% of the now-adult subjects confirmed that the localisation of their pain changed as they grew up. This confirms that migraine should be seen by clinicians as a genetically determined disease. In addition, about 76.4% of the subjects confirmed the persistence of migraines at the transition from childhood to adulthood. The results of the study clearly show that the early onset of migraine (occurring below the age of 6 years) is an extremely important risk factor in the persistence of migraines into adulthood, and an important point to emphasise is that this is independent of the gender of the patient [9].

The only possible way to prevent migraines in adults is to administer appropriate pharmacotherapy to children as early as possible when severe headaches are reported. Scott et al. conducted a study on a group of 205 children and adolescents whom they followed for 3 years. Patients were given amitriptyline, topiramate or placebo, and with each successive month the number of migraine patients reported decreased: 189 initially, 189 after 6 months, 182 after 12 months, 165 after 24 months and 155 after 36 months. While on the medication, subjects said they saw a significant reduction in days with severe headache [72]. In 1955, Bille B et al conducted a 40-year follow-up of 9,000 patients reporting having migraines and no migraines, starting when they were children. After 16 years of follow-up, about one-third of the subjects reported a recurrence of migraines after a 6-year break from attacks. After 30 years, about 53% of the patients confirmed the continued presence of migraines. After a 40-year follow-up, the researchers observed migraine attacks in their children, who also began to report recurrent headaches. By the time they passed the age of 50, about half still reported further migraine complaints. In about one-third of the subjects, despite the cessation of migraines, a spontaneous return of migraines was observed after 10 years [73].

Diagnostic difficulties may also be related to the inability of the children to name the symptoms they experience [3, 74, 75]. The currently-used ICHD-3 criteria have limitations, especially in children. Children newly-diagnosed with migraine using the Morningness-Eveningness Questionnaire (MEQ-SA) [76] were divided into 5 groups depending on the type of chronotype. The results showed a relationship between the chronotype and the course of migraine. It was observed that those who got up earlier had significantly fewer migraine attacks, but a longer course of illness compared to people who got up early in the morning. The chronotype affects the number and length of migraine episodes, but does not affect the intensity of experienced symptoms [3, 76]. Sleep disorders such as nightmares, sleep talking, sleepwalking and bruxism, are included in the ICHD-3 [3] and are treated as an early manifestation of migraine disorders in childhood and a component of the 'childhood migraine syndrome'; therefore, the treatment of sleep disorders is a potential way to treat migraine disorders, but further research is needed [2, 9, 48, 76].

Other potential lifestyle factors may also influence the incidence of migraine in children. These include physical activity, which can be a trigger of migraine attacks; however, regular training, appropriately selected for the needs of individuals, can have a potentially preventive effect [74], similarly, specific diets are associated with both increased or decreased frequency of migraine episodes [77, 78].

The psychological and environmental aspects cannot be overlooked in the diagnostic process, and psychotherapy should be considered as one of the strategies to prevent migraine recurrences [79, 80].

Bhurat et al. conducted a study on a group of 35 children aged 5–18 suffering from migraine, in which they examined the level of magnesium in the blood serum and its impact on the occurrence of migraine. None of the subjects had hypomagnesaemia requiring supplementation. In the entire study group, the median serum magnesium level was 2.0 (2.0; 2.1) mg/dl, and in the control group – 2.2 (1.9; 2.2) mg/dl. These results did not differ statistically significantly. In the age group of 10–18 years, however, the results were 2.0 (1.9; 2.1) mg/dl in the study group and 2.2 (2.0; 2.2) mg/dl in the control group. This was a statistically significant difference. The relationship discovered between low serum magnesium levels and the occurrence of migraine in adolescents may be a starting point for future research on the causal treatment of migraine [80].

Studies have shown that a non-standard treatment method – acupuncture, reduces the frequency of migraine episodes among children and adults alike, primarily by stimulating the activity of the opioid system [81].

Topiramate, which is the only drug that can be used to prevent migraine attacks in the paediatric population, in a randomized trial by Powers et al. showed an effect similar to that of a placebo, with no statistically significant differences; therefore, there is a need to search for other drugs that will work more effectively in the causal treatment of the problem discussed in the review [57].

## CONCLUSIONS

Migraines in children represent a difficult disease entity both diagnostically and therapeutically. To date, no

significant changes have been demonstrated on imaging studies in children and the symptoms themselves may be uncharacteristic. Further research is needed to consider and implement new drugs. It is important to remember that untreated migraine in childhood will have serious consequences in adulthood; hence it is important not to underestimate the somatic symptoms reported by children.

## REFERENCES

- Dodick DW. Migraine. *Lancet*. 2018 Mar 31;391(10127):1315–1330. [https://doi.org/10.1016/S0140-6736\(18\)30478-1](https://doi.org/10.1016/S0140-6736(18)30478-1)
- Abu-Arafeh I, Gelfand AA. The childhood migraine syndrome. *Nat Rev Neurol*. 2021 Jul;17(7):449–458. <https://doi.org/10.1038/s41582-021-00497-6>
- Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018 Jan;38(1):1–211. <https://doi.org/10.1177/0333102417738202>
- Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. *Neurol Clin*. 2019 Nov;37(4):631–649. <https://doi.org/10.1016/j.ncl.2019.06.001>
- Al Khalili Y, Asuncion RMD, Chopra P. Migraine Headache in Childhood. 2023 Mar 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. PMID: 32491745
- Raieli V, D'Amico A, Piro E. Migraine in Children Under 7 Years of Age: a Review. *Curr Pain Headache Rep*. 2020 Dec 16;24(12):79. <https://doi.org/10.1007/s11916-020-00912-5>
- Ursitti F, Valeriani M. Migraine in childhood: Gender differences. *Eur J Paediatr Neurol*. 2023 Jan;42:122–125. <https://doi.org/10.1016/j.ejpn.2023.01.002>
- Youssef PE, Mack KJ. Episodic and chronic migraine in children. *Dev Med Child Neurol*. 2020 Jan;62(1):34–41. <https://doi.org/10.1111/dmcn.14338>
- Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children: association with school performance. *Neurology*. 2012 Oct 30;79(18):1881–8. <https://doi.org/10.1212/WNL.0b013e318271f812>
- Guidetti V, Cerutti R, Faedda N, Natalucci G. Migraine in childhood: an organic, biobehavioral, or psychosomatic disorder? *Neurol Sci*. 2019 May;40(Suppl 1):93–98. <https://doi.org/10.1007/s10072-019-03827-1>
- Straube A, Heinen F, Ebinger F, et al. Headache in school children: prevalence and risk factors. *Dtsch Arztebl Int*. 2013 Nov 29;110(48):811–8. <https://doi.org/10.3238/arztebl.2013.0811>
- Lagman-Bartolome AM, Lay C. Pediatric migraine variants: a review of epidemiology, diagnosis, treatment, and outcome. *Curr Neurol Neurosci Rep*. 2015 Jun;15(6):34. <https://doi.org/10.1007/s11910-015-0551-3>
- Nosedá R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. *Pain*. 2013 Dec;154 Suppl 1:S44–53. <https://doi.org/10.1016/j.pain.2013.07.021>
- Ferrari MD, Klever RR, Terwindt GM, et al. Migraine pathophysiology: lessons from mouse models and human genetics. *Lancet Neurol*. 2015 Jan;14(1):65–80. [https://doi.org/10.1016/S1474-4422\(14\)70220-0](https://doi.org/10.1016/S1474-4422(14)70220-0)
- Winner P, Linder S, Hershey AD. Consistency of response to sumatriptan/naproxen sodium in a randomized placebo-controlled, cross-over study for the acute treatment of migraine in adolescence. *Headache* 2015;55:519–528. <https://doi.org/10.1111/head.12555>
- Maniyar FH, Sprenger T, Monteith T, et al. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain*. 2014 Jan;137(Pt 1):232–41. <https://doi.org/10.1093/brain/awt320>
- Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case-control study. *Neurology*. 2002 Feb 12;58(3):422–7. <https://doi.org/10.1212/wnl.58.3.422>
- Nosedá R, Kainz V, Borsook D, Burstein R. Neurochemical pathways that converge on thalamic trigeminovascular neurons: potential substrate for modulation of migraine by sleep, food intake, stress and anxiety. *PLoS One*. 2014 Aug 4;9(8):e103929. <https://doi.org/10.1371/journal.pone.0103929>
- Borsook D, Maleki N, Becerra L, McEwen B. Understanding migraine through the lens of maladaptive stress responses: a model disease of allostatic load. *Neuron*. 2012 Jan 26;73(2):219–34. <https://doi.org/10.1016/j.neuron.2012.01.001>
- Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci U S A*. 2001 Apr 10;98(8):4687–92. <https://doi.org/10.1073/pnas.071582498>
- Lippman CW. Certain hallucinations peculiar to migraine. *J Nerv Ment Dis*. 1952 Oct;116(4):346–51. <https://doi.org/10.1097/00005053-195210000-00009>
- Basedau H, Sturm LM, Mehnert J, et al. Migraine monoclonal antibodies against CGRP change brain activity depending on ligand or receptor target – an fMRI study. *Elife*. 2022 May 23;11:e77146. <https://doi.org/10.7554/eLife.77146>
- Edvinsson L, Haanes KA, Warfvinge K, et al. CGRP as the target of new migraine therapies – successful translation from bench to clinic. *Nat Rev Neurol*. 2018 Jun;14(6):338–350. <https://doi.org/10.1038/s41582-018-0003-1>
- Zhang Q, Han X, Wu H, et al. Dynamic changes in CGRP, PACAP, and PACAP receptors in the trigeminovascular system of a novel repetitive electrical stimulation rat model: Relevant to migraine. *Mol Pain*. 2019 Jan-Dec;15:1744806918820452. <https://doi.org/10.1177/1744806918820452>
- Johansson SE, Abdolizadeh B, Sheykhzade M, et al. Vascular pathology of large cerebral arteries in experimental subarachnoid hemorrhage: Vasoconstriction, functional CGRP depletion and maintained CGRP sensitivity. *Eur J Pharmacol*. 2019 Mar 5;846:109–118. <https://doi.org/10.1016/j.ejphar.2019.01.007>
- Basedau H, Oppermann T, Gundelwein Silva E, et al. Characterization of trigeminal C-fiber reactivity through capsaicin-induced release of calcitonin gene-related peptide. *Headache*. 2023 Mar;63(3):353–359. <https://doi.org/10.1111/head.14471>
- Nowaczewska M, Straburzyński M, Waliszewska-Prosół M, et al. Cerebral Blood Flow and Other Predictors of Responsiveness to Erenumab and Fremanezumab in Migraine-A Real-Life Study. *Front Neurol*. 2022 May 17;13:895476. <https://doi.org/10.3389/fneur.2022.895476>
- Mulder IA, Li M, de Vries T, et al. Anti-migraine Calcitonin Gene-Related Peptide Receptor Antagonists Worsen Cerebral Ischemic Outcome in Mice. *Ann Neurol*. 2020 Oct;88(4):771–784. <https://doi.org/10.1002/ana.25831>
- Giani L, Proietti Cecchini A, Leone M. Anti-CGRP in cluster headache therapy. *Neurol Sci*. 2019 May;40(Suppl 1):129–135. <https://doi.org/10.1007/s10072-019-03786-7>
- Nisar A, Ahmed Z, Yuan H. Novel Therapeutic Targets for Migraine. *Biomedicines*. 2023 Feb 15;11(2):569. <https://doi.org/10.3390/biomedicines11020569>
- Brumm K, Walenski M, Haist F, et al. Functional magnetic resonance imaging of a child with Alice in Wonderland syndrome during an episode of microspia. *J AAPOS*. 2010 Aug;14(4):317–22. <https://doi.org/10.1016/j.jaaapos.2010.03.007>
- Gencoglu EA, Alehan F, Erol I, et al. Brain SPECT findings in a patient with Alice in Wonderland syndrome. *Clin Nucl Med*. 2005 Nov;30(11):758–9. <https://doi.org/10.1097/01.rlu.0000182278.13389.a3>
- Morland D, Wolff V, Dietemann JL, et al. Robin Hood caught in Wonderland: brain SPECT findings. *Clin Nucl Med*. 2013 Dec;38(12):979–81. <https://doi.org/10.1097/RLU.0000000000000230>
- Sampaio Rocha-Filho PA, Gherpelli JLD. Premonitory and Accompanying Symptoms in Childhood Migraine. *Curr Pain Headache Rep* 2022;26:151–163. <https://doi.org/10.1007/s11916-022-01015-z>
- Cuvellier JC, Mars A, Vallée L. The prevalence of premonitory symptoms in paediatric migraine: a questionnaire study in 103 children and adolescents. *Cephalalgia*. 2009;29:1197–201. <https://doi.org/10.1111/j.1468-2982.2009.01854>
- Karsan N, Prabhakar P, Goadsby PJ. Characterising the premonitory stage of migraine in children: a clinic-based study of 100 patients in a specialist headache service. *J Headache Pain*. 2016;17:94. <https://doi.org/10.1186/s10194-016-0689-7>
- Petrusic I, Pavlovski V, Vucinic D, et al. Features of migraine aura in teenagers. *J Headache Pain* 2014;15:87. <https://doi.org/10.1186/1129-2377-15-87>
- Ahmed M, Boyd C, Vavilikolanu R, et al. Visual symptoms and childhood migraine: Qualitative analysis of duration, location, spread, mobility, colour and pattern. *Cephalalgia*. 2018;38:2017–25. <https://doi.org/10.1177/0333102418766872>
- Blom JD. Alice in Wonderland syndrome: A systematic review. *Neurol Clin Pract*. 2016 Jun;6(3):259–270. <https://doi.org/10.1212/CPJ.0000000000000251>
- Genizi J, Khourieh Matar A, Zelnik N, et al. Frequency of pediatric migraine with aura in a clinic-based sample. *Headache*. 2016 Jan;56(1):113–7. <https://doi.org/10.1111/head.12741>



41. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1–211. <https://doi.org/10.1177/0333102417738202>
42. Li BU. Managing cyclic vomiting syndrome in children: beyond the guidelines. Eur J Pediatr. 2018 Oct;177(10):1435–1442. <https://doi.org/10.1007/s00431-018-3218-7>
43. Mamouri O, Cuvellier JC, Duhamel A, et al. Postdrome symptoms in pediatric migraine: a questionnaire retrospective study by phone in 100 patients. Cephalalgia. 2018;38:943–8. <https://doi.org/10.1177/0333102417721132>
44. Gelfand AA. Episodic syndromes that may be associated with migraine: a.k.a. “the childhood periodic syndromes”. Headache. 2015;55(10):1358–64. <https://doi.org/10.1111/head.12624>
45. Rothner AD, Parikh S. Headache currents: migraine variants or episodic syndromes that may be associated with migraine and other unusual pediatric headache syndromes. Headache. 2015;56(1):206–14. <https://doi.org/10.1111/head.12750>
46. Sabino L, Marino S, Falsaperla R, et al. Celiac disease and headache in children: a narrative state of the art. Acta Biomed. 2020 Sep 7;91(3):e2020056. <https://doi.org/10.23750/abm.v91i3.8224>
47. Miller JA, Missmer SA, Vitonis AF, et al. Prevalence of migraines in adolescents with endometriosis. Fertil Steril. 2018 Apr;109(4):685–690. <https://doi.org/10.1016/j.fertnstert.2017.12.016>
48. Walter SM, Dai Z, Wang K. Obesity, Migraine, and Overlapping Comorbidities in a Rural Pediatric Population. J Neurosci Rural Pract. 2021 Jul;12(3):524–529. <https://doi.org/10.1055/s-0041-1727574>
49. Zhao YJ, Lim JY, Wong PS. Diagnosis and Management of Headaches in the Emergency Department (ED) in Adults and Children. Neurol India 2021;69, Suppl S1:173–82. <https://doi.org/10.4103/0028-3886.315977>
50. Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol. 2021;17(8): 501–514. <https://doi.org/10.1038/s41582-021-00509-5>
51. de Tommaso M. An update on EEG in migraine. Expert Rev Neurother. 2019 Aug;19(8):729–737. <https://doi.org/10.1080/14737175.2019.1586534>
52. Webb ME, Amoozegar F, Harris AD. Magnetic Resonance Imaging in Pediatric Migraine. Canad J Neurol Sci. 2019;46(6):653–665. <https://doi.org/10.1017/cjn.2019.243>
53. Koch T, Oakley CB. Pediatric migraine: Diagnostic criteria and treatment. Contemp. Pediatr. June 2018;35(6):22.
54. Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents, Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. Sep 2019;93(11):487–499. doi:10.1212/WNL.00000000000008095
55. O'Brien H, Kabbouche MA, Kacperski J, et al. Treatment of Pediatric Migraine. Curr Treat Options Neurol. 2015;17(1). <https://doi.org/10.1007/s11940-014-0326-1>
56. Gross EC, Lisicki M, Fischer D, et al. The metabolic face of migraine – from pathophysiology to treatment. Nat Rev Neurol. 2019 Nov;15(11):627–643. <https://doi.org/10.1038/s41582-019-0255-4>
57. Powers SW, Coffey CS, Chamberlin LA, et al. Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine. N Engl J Med. 2017 Jan 12;376(2):115–124. <https://doi.org/10.1056/NEJMoa1610384>
58. Powers SW, Kashikar-Zuck SM, Allen JR, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. JAMA 2013;310:2622–2630. <https://doi.org/10.1001/jama.2013.282533>
59. Amanat M, Togha M, Agah E, et al. Cinnarizine and sodium valproate as the preventive agents of pediatric migraine: A randomized double-blind placebo-controlled trial. Cephalalgia. 2020;40(7):665–674. <https://doi.org/10.1177/0333102419888485>
60. Borner C, Urban G, Beaulieu LD, et al. The bottom-up approach: Non-invasive peripheral neurostimulation methods to treat migraine: A scoping review from the child neurologist's perspective. Eur J Pediatr Neurol. 2021;32:16–28. <https://doi.org/10.1016/j.ejpn.2021.02.008>
61. Papetti L, Sforza G, Tullo G, et al. Tolerability of Palmitoylethanolamide in a Pediatric Population Suffering from Migraine: A Pilot Study. Pain Res Manag. 2020 Apr 24;2020:3938640. <https://doi.org/10.1155/2020/3938640>
62. Edvinsson L. Role of CGRP in Migraine. Handb Exp Pharmacol. 2019;255:121–130. [https://doi.org/10.1007/164\\_2018\\_201](https://doi.org/10.1007/164_2018_201)
63. Negro A, Martelletti P. Gepants for the treatment of migraine. Expert Opin Investig Drugs. 2019 Jun;28(6):555–567. <https://doi.org/10.1080/13543784.2019.1618830>
64. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the Treatment of Migraine. N Engl J Med. 2019 Dec 5;381(23):2230–2241. <https://doi.org/10.1056/NEJMoa1813049>
65. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. Lancet. 2019 Aug 31;394(10200):737–745. [https://doi.org/10.1016/S0140-6736\(19\)31606-X](https://doi.org/10.1016/S0140-6736(19)31606-X)
66. Szperka CL, VanderPluym J, Orr SL, et al. Recommendations on the use of anti-CGRP monoclonal antibodies in children and adolescents. Headache. 2018;58(10):1658–69. <https://doi.org/10.1111/2Fhead.13414>
67. Marshall A, Lindsay R, Clementi MA, et al. Outpatient Approach to Resistant and Refractory Migraine in Children and Adolescents: a Narrative Review. Curr Neurol Neurosci Rep. 2022;22:611–624. <https://doi.org/10.1007/s11910-022-01224-4>
68. Esparham A, Stark-Inbar A, Jekel L, et al. Acute Treatment of Migraine in Adolescents: Real-World Analysis of Remote Electrical Neuromodulation (REN). Pediatr Neurol. 2023;142:51–55 <https://doi.org/10.1016/j.pediatrneurol.2023.02.008>
69. Barbanti P, Fofi L, Aurili C, et al. Ketogenic diet in migraine: rationale, findings and perspectives. Neurol Sci. 2017; 38 (Suppl 1):111–115. <https://doi.org/10.1007/s10072-017-2889-6>
70. Tarantino S, Papetti L, Di Stefano A, et al. Anxiety, Depression, and Body Weight in Children and Adolescents With Migraine. Front Psychol. 2020 Oct 28;11:530911. <https://doi.org/10.3389/fpsyg.2020.530911>
71. Papetti L, Moavero R, Ferilli MAN, et al. Truths and Myths in Pediatric Migraine and Nutrition. Nutrients. 2021;13(8):2714. <https://doi.org/10.3390/nu13082714>
72. Papetti L, Salfa I, Battan B, et al. Features of Primary Chronic Headache in Children and Adolescents and Validity of Icdh 3 Criteria. Front Neurol. 2019 Feb 15;10:92. <https://doi.org/10.3389/fneur.2019.00092>
73. Viticchi G, Falsetti L, Paolucci M, et al. Influence of chronotype on migraine characteristics. Neurol Sci. 2019 Sep;40(9):1841–1848. <https://doi.org/10.1007/s10072-019-03886-4>
74. Amin FM, Aristeidou S, Baraldi C, et al. European Headache Federation School of Advanced Studies (EHF-SAS). The association between migraine and physical exercise. J Headache Pain. 2018 Sep 10;19(1):83. <https://doi.org/10.1186/s10194-018-0902-y>
75. Hindiyyeh NA, Zhang N, Farrar M, et al. The Role of Diet and Nutrition in Migraine Triggers and Treatment: A Systematic Literature Review. Headache. 2020 Jul;60(7):1300–1316. <https://doi.org/10.1111/head.13836>
76. Minen MT, Begasse De Dhaem O, et al. Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psychiatry. 2016 Jul;87(7):741–9. <https://doi.org/10.1136/jnnp-2015-312233>
77. Garnefski N, van Rood Y, de Roos C, et al. Relationships Between Traumatic Life Events, Cognitive Emotion Regulation Strategies, and Somatic Complaints. J Clin Psychol Med Settings. 2017 Jun;24(2):144–151. <https://doi.org/10.1007/s10880-017-9494-y>
78. Afifi TO, MacMillan HL, Boyle M, et al. Child abuse and physical health in adulthood. Health Rep. 2016 Mar 16;27(3):10–8. PMID: 26983007
79. Tietjen GE, Karmakar M, Amialchuk AA. Emotional Abuse History and Migraine Among Young Adults: A Retrospective Cross-Sectional Analysis of the Add Health Dataset. Headache. 2017 Jan;57(1):45–59. <https://doi.org/10.1111/head.12994>
80. Bhurat R, Premkumar S, Manokaran RK. Serum Magnesium Levels in Children With and Without Migraine: A Cross-Sectional Study. Indian Pediatr. 2022 Aug 15;59(8):623–625. PMID: 35751375
81. Liao CC, Chien CH, Shih YH, et al. Acupuncture Is Effective at Reducing the Risk of Stroke in Patients with Migraines: A Real-World, Large-Scale Cohort Study with 19-Years of Follow-Up. Int J Environ Res Public Health. 2023 Jan 17;20(3):1690. <https://doi.org/10.3390/ijerph20031690>