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Migraine in children population - systemic review

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Abstract

Introduction and objective: Migraine constitutes the main reason for acute and recurrent headache among children globally. It is a primary headache syndrome that affects from 3 up to 10% of paediatric population. The frequency of migraine increases with age up to puberty.

The aim of this study is to systemize recent knowledge about migraine in children. The information used in the presented analysis was obtained by searching academic research databases: Google Scholar and PubMed.

An abbreviated description of the state of knowledge: The exact pathogenesis of migraine remains unknown, but involvement of nervous system, cardiovascular system, genetic predisposition and environmental factors are considered in the development of disease. Symptoms of migraine vary between individuals and can be wide-ranging. They may resemble disorders such as tension headache, cluster headache, epilepsy, brain tumour or ischemic stroke. The diagnostic process is based on anamnesis, and may therefore be challenging in children because of difficulties related to communication. Symptom-relieving therapy of migraine is well-established in contrast to pharmacological prophylactic treatment which is not sufficiently evidence-based.

Summary: Migraine remains a global problem in the paediatric population. The condition is associated not only with physical pain, but also it leads to many long-term complications such as emotional problems and social disruption. Lack of safe and effective preventive medical therapies is a driving factor to improve trials of migraine treatment in the future.

Key words: migraine, children, diagnosis, treatment

Introduction and objectives

Migraine is a primary headache syndrome and remains a leading cause of disability worldwide [1,2]. Among children, migraine constitutes the most common reason for acute and recurrent headache. Migraine affects 3-10% of children and increases in prevalence with age up to puberty, while other studies have described the prevalence of migraine as up to 28% of older teenagers. Migraine frequently starts in childhood and adolescence. Clinical features of this syndrome in the paediatric population are specific and unique, which furthermore can evolve with age. The International Classification of Headache Disorders (ICDH) describes differences in symptoms in both paediatric and adults suffering from migraine. In addition to this, migraine can have a substantial effect on a child's quality of life, family time and also may affect everyday activities like socializing with peers and cause difficulties with school [3,4,5,6]. Symptoms of migraine are wide-ranging. Younger groups of patients tend to experience bilateral frontal headaches, commonly associated with nausea, abdominal pain, vomiting, phonophobia and excessive daytime sleepiness. On the other hand, aura and bitemporal headache are more characteristic in older adolescents [3,6]. Over the years, many treatment strategies have been developed for migraine in adults, in comparison to the paediatric population, in which only some of the medications are considered safe and have been approved. Treatment is usually based on symptom-relieving therapy and aims to alleviate clinical features such as nausea, photophobia, phonophobia and also headache control. Nevertheless, prophylactic medication strategies focus on providing freedom from pain and reducing recurrence [7,8]. We present a review article in which we aim to systemize recent knowledge about the pathogenesis of the disease, its prevalence among paediatric patients, and discuss potential treatment options for this patient population. The information used in the presented analysis was obtained by searching academic research databases: Google Scholar and PubMed. The strategy of searching was based on the following keywords: migraine, children, diagnosis, treatment. The available articles have been selected in terms of their content value and thematic connection with the topic of this article.

Epidemiology and pathogenesis

Migraine is a primary headache syndrome and among children constitutes the most common reason for acute and recurrent headache. The condition has a slight predominance in boys during the pre-pubertal years, while in girls it is more predominant in adolescence. The age of onset of the disease varies and the overall occurrence of migraine increases throughout adolescence into young adulthood. The prevalence of episodic migraine is estimated to be at 2 to 5% of preschool children, 10% of school-aged children, and 20 to 30 % of adolescent females [6]. A recent Saudi Arabia research study including 23 papers, revealed that the prevalence of migraine among schoolchildren (6 to 18 years old) ranged between 7.1% and 13.7% [9]. In Poland, 2351 students aged 15 to 19 years old were included in a study, of which 28% suffered from migraine. However, migraine with aura was noted in 9% of cases and without aura in 19% [10]. A group of 4387 Italian students (48.4% males) aged 11,13 and 15 years old were included into a study, in which 40% of participants reported presence at least one headache a week. There was a correlation between teacher unfairness towards the students and headache occurrence. Moreover, prevalence of headache increased with the age of the student [11]. Studies have shown females to be more frequent group of children suffering from migraine [9,10,11]. The majority of patients featured in research studies had a positive family history of migraine [3,12].

Pathophysiology

Understanding the pathophysiology mechanisms of migraine remains challenging. The mechanism is presumably the same in both children and adult populations. Migraine is considered to be based on the interaction of the neural and vascular systems, including cortical spreading depression and trigeminal vascular activation [6]. Data has shown that the most common migraine triggers include stress or subsequent relaxation, fasting or skipping a meal, sleep changes, ovarian hormone changes (including menstruation and oral contraception), weather changes (including certain winds or hypoxia), physical activity, alcohol consumption, strong odours (especially perfume or cigarette smoke), intense light (especially bright or blue light) and loud noises [13]. Some of the mentioned triggers such as physical activity, lack of sleep or skipping a meal have a correlation with metabolism, also including hormonal changes. This may be associated with increased oxidative stress in the Central Nervous System and changes in mitochondrial metabolism. The migraine attack threshold of an individual is likely to be determined by metabolic and endocrinological anomalies, presumably in combination with abnormalities in cerebral responsiveness. Moreover, the severity of the disease is likely to be determined by the cumulative number of abnormalities, in conjunction with unfavourable environmental factors. Genetic inheritance and the environmental effects also constitute the risk factors of developing migraine. Genetic influence may reach 60-70%, with environmental influence completing the remaining proportion. There are multiple genes responsible for development of the disorder. Migraine expression mainly depends on neurotransmission changes between neurons, and between neurons and blood vessels. Nevertheless, the genetic risk factors of migraine are still widely unknown. In summary, the basis of the migraine is currently considered to lay with adaptive response that affects patients with a genetic predisposition, and a mismatch between the brain’s energy reserve and workload [6,14].

Diagnostic criteria

Diagnosis of migraine in children is mainly based on anamnesis [15]. Obtained information must include not only age at onset of headache, duration and frequency of episodes, pain characteristics, but also accompanying symptoms [16]. In paediatric patients, identification of migraine may be challenging due to the subjective nature of its symptoms, making them difficult to evaluate. According to the International Headache Society (IHS) migraine is defined as a recurrent headache that occurs with or without aura and lasts from 2 to 48 hours [4]. Commonly used diagnostic criteria for migraine with (Table 1) and without aura (Table 2) have been developed by the IHS. The diagnostic criteria for migraine remains similar in both the adult and paediatric population [17,18].

Table 1. Diagnostic criteria for migraine with aura

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms: - visual - sensory - speech and/or language - motor - brainstem - retinal
C. At least three of the following (six) characteristics: - at least one aura symptom spreads gradually over ≥5 minutes - two or more aura symptoms occur in succession - each individual aura symptom lasts 5-60 minutes - at least one aura symptom is unilateral - at least one aura symptom is positive (scintillations, pins and needles) - the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis

Table 2. Diagnostic criteria for migraine without aura

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 2-72 hr (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics: - bilateral location - pulsating quality - moderate to severe pain intensity - aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following: - nausea and/or vomiting - photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Symptoms

Migraine is a disease of recurring, pulsating headaches with wide ranging intensity (from moderate to severe). They are characterized by a combination of multiple symptoms such as vomiting, photophobia, phonophobia, which worsen during physical activity. The

characteristics of migraine headache in children are different to that in adults [3,19] (Table 3). Autonomic symptoms are also common. These include: facial redness, a feeling of fullness in the ears, conjunctival hyperaemia, tearing and drooping eyelids. Among children up to 5 years of age, migraine attacks can manifest as irritability, rocking and looking for a dark room to sleep [3]. Young women of adolescent age may suffer from migraines related to menstruation. Headache has a very negative impact on the quality of life of patients. It may have detrimental effects on life at school, with family and the patient's emotional functioning [20]. Children suffering from migraines often have more absences from school, poorer academic performance, and limited relationships with their peers. It has also been shown that children with migraines show a higher level of pain catastrophizing. Recurrent attacks of pain may be associated with the development of depression and internalisation [21]. Among children and adolescents with migraine, one third of patients suffer from migraine with aura, which may precede or accompany the headache. Patients will often experience aura for the first time at the age of 8. It begins gradually over 5 minutes and last up to 60 minutes [3,22]. Visual impairment (the presence of unformed black and white patterns or scotoma), as the most common symptom, affects > 90% of patients. However, aura can manifest itself in several distinct ways, such as paraesthesia or aphasic speech disturbance. Brainstem symptoms (dysarthria or vertigo), motor weakness and retinal symptoms (such as repeated monocular visual disturbances) may also occur in the course of aura. There are different types of aura: visual, sensory, speech or language, motor, retinal and brainstem [3,16,23]. Migraine in children is characterized by a frequent occurrence of predictive symptoms. The prodromal phase precedes the onset of aura and headache by several hours. The most common change that might be noticed is a change in mood. The child may be agitated or, on the contrary, depressed and sad. In addition, the patient may experience difficulty in thinking, have trouble concentrating, irritability, and confusion. Other very common symptoms that children may experience are tiredness and neck stiffness. It was noticed that in some paediatric patients frequent yawning, gastrointestinal disorders, dizziness, thirst, hunger, polyuria, pallor, feeling hot, drowsiness or tearfulness can also be observed [21,24]. When the migraine attack is over, many patients experience postdromal symptoms, which can last up to 48 hours. After the headache phase, children are most often exhausted, lost and lethargic. They may experience fatigue, difficulty in concentrating and neck stiffness or, on the contrary, they may be agitated [3,16,21]. Another phenomenon unique to children is the occurrence of migraine syndromes. These are paroxysmal periodic syndromes that may precede the development of migraine by several years. It has been investigated that each episode of a childhood syndrome increases the risk of developing migraine by over 50% [19]. Such diseases include cyclic vomiting syndrome, abdominal migraine, mild paroxysmal vertigo and mild paroxysmal torticollis [25,26]. 34-90% of patients diagnosed with abdominal migraine have a family history of first-degree relatives with migraine headaches. Moreover, it has been proven that abdominal migraine is a precursor to migraine [27,28].

Table 3. Differences between migraine in children and adults

	Children	Adults
Typical duration	2-72 hours (usually < 4 hours)	4-72 hours
Attacks lasting 30 minutes	Often	Never
Pain localization	Usually bilateral frontotemporal	Usually unilateral
Pain intensity	Milder	From moderate to severe
Phonophobia	Rare	More frequent
Vegetative signs	More frequent	Rare
Migraine-related syndromes	More frequent	Rare

Treatment

Treatment of migraine in children is based on a multi-tiered approach [29] (Table 4). There are many medications used in the treatment of migraine in adults, although only some of them have been approved for use in paediatric patients. The aim of symptom-relieving therapy is to alleviate clinical manifestations such as nausea, phonophobia or photophobia and to reduce head pain. On the other hand, prophylactic medications concentrate on reducing the frequency and severity of the attacks [7]. Early diagnosis and proper identification of factors that induce the attacks are crucial for an effective therapeutic process, combined with avoiding triggers [18,30]. During a migraine attack, potential treatment options include intravenous rehydration, antiemetics, analgesics, ergot-based therapies and triptans (Table 4). Future research on calcitonin gene-related peptide (CGRP) may elucidate other therapeutic option through the mechanism of vasodilation of pial, meningeal and extracranial cephalic arteries [30]. Despite the range of treatment options for migraine, the first line drug therapy for moderate and severe cases is based on non-steroidal anti-inflammatory drugs used in conjunction with triptans [31,32]. Moreover, dihydroergotamine can be used in hospital to induce vasoconstriction in patients suffering from intractable migraine that has not responded to previous medication [33]. Non-pharmacological prophylactic treatment consists of psychological therapies such as cognitive-behavioural therapy, biofeedback program and relaxation training or administration of nutraceuticals (hydroxytryptophan, magnesium or riboflavin) [30, 34]. If these forms of treatment remain ineffective, pharmacological prophylactic treatment may be indicated, particularly when the frequency of attacks exceeds 4 attacks per month or the response to the symptomatic treatment is not sufficient. There are many commonly used preventive drugs such as calcium channel blockers, non-selective beta adrenoceptor antagonists, tricyclic antidepressants and antiepileptic drugs. Another group of medications also administered preventively are serotonin modulators (Table 4). Pharmacological treatment is known to cause multiple side-effects, the most common of which are sedation, dizziness, nausea and fatigue [35]. Recent research has indicated that there are no significant long-term effects associated with pharmacological migraine prophylaxis [36]. This may act as a driving force to improve preventive therapeutic options and to develop more effective treatment trials in the future [37].

Table 4. Approach to the treatment of migraine

First tier – Lifestyle modification	- Good sleep hygiene - Well-balanced diet - Avoidance of triggers - Hydration - Exercises
Second tier – Integrative therapies	- Psychological therapies (such as cognitive-behavioural therapy, biofeedback or stress management techniques) - Administration of nutraceuticals (such as hydroxytryptophan, magnesium or riboflavin)

Third tier – Pharmacologic treatment	Acute treatment - Intravenous rehydration - Antiemetics (Intravenous prochlorperazine at the dose of 0.15 mg/kg, the maximum dose must not exceed 10 mg) (Oral/intravenous metoclopramide at the dose of 0.13-0.15 mg/kg with a maximum of 10 mg/dose) - Analgesics (Ibuprofen at the dose of 7.5-10 mg/kg) (Acetaminophen at the dose of 15 mg/kg) - Ergot-based therapies (Dihydroergotamine at the dose of 0.1-0.2 mg) - Triptans (Sumatriptan in nasal spray at the dose of 5, 10 or 20 mg in each nostril or 25, 50, 100 mg orally or 3-6 mg subcutaneously) (Rizatriptan at the dose of 5 mg administered orally, used in 12-17 years old patients) (Zolmitriptan at the dose of 2.5 or 5 mg administered orally, used in 12-17 years old patients)	Commonly used preventive treatment - Calcium channel blockers (Flunarizine at the dose of 5-10 mg/day, preferred in patients with coexisting anxiety and insomnia) - Non-selective beta adrenoceptor antagonist (Propranolol at the dose of 3mg/kg/day, preferred in patients with history of hypertension) - Tricyclic antidepressants (Amitriptyline at the dose of 1mg/kg/day, preferred in not-obese patients with coexisting depression or insomnia) - Antiepileptic drugs (Sodium valproate at the dose of 30 mg/kg/day, used especially in male patients with history of psychosis) (Topiramate at the dose of 2-3 mg/kg/day, preferred in overweight patients with no history of cognitive dysfunction) - Serotonin modulators (Pizotifen at the dose of 1.5 mg/day, used especially in no obese patients with history of depression or insomnia) (Cyproheptadine at the dose of 0.2–0.4 mg/kg/day preferred in patients with no asthma)
Fourth tier – Other treatment	- Onabotulinum toxin A - Nerve blocks	- Neurostimulation - Surgery

Differentiation

In order to diagnose a migraine headache, other potential causes of the headache have to be ruled out. According to the 3rd edition of ICDH, headache can be divided into primary, secondary, neuropathic and other. Primary headache includes conditions such as tension headache, trigeminal autonomic headaches (such as cluster headache), pain caused by exercise, stress, temperature, and persistent daily headache. Secondary headache may be caused by infections, toxic substances, injuries, vascular and psychiatric disorders [38]. If a secondary cause of pain is suspected, neuroimaging is recommended [39]. Furthermore primary headache is responsible for the vast majority of headaches, and its diagnosis is based on the IHS diagnostic criteria [40]. Firstly, migraine should be differentiated from the extremely frequent tension headache. Tension headaches are described as dull, compression, head-crushing pain, radiating to the back of the head or forehead, and in many cases extending to the back of the neck. Most patients have a rare episodic form that generally do

not require treatment [41]. The clinical picture of cluster headache (CH) and migraine is usually different, but they share several phenotypic similarities such as severe unilateral pain and some co-existing symptoms including aura. Cluster pain attacks are accompanied by autonomic symptoms on the same side such as lacrimation, runny nose, brow sweating, miosis, and ptosis. Migraine patients usually have only one symptom and in contrast to patients suffering from CH, they have bilateral symptoms, a milder course of disease and a lower frequency of episodes. Unlike migraines, attacks happen at night, and seasonally in spring and autumn. There are similar triggers for migraine and CH attacks, such as stress, sleep, weather changes, and alcohol consumption. CH and migraine differ in their prevalence in men and women. Cluster pain mainly affects men, while migraine is two to three times more frequent in women [42]. Migraine with aura is related with visual manifestations such as blurred vision and appearance of black dots or scotoma in the visual field. Other primary and secondary headaches may often also cause discomfort and pain in or around the eye. By taking a careful history and carrying the appropriate diagnostic tests, it is possible to distinguish primary headaches from potentially sinister causes (stroke, giant cell arteritis, orbital cellulitis or expanding aneurysm) [3,43]. Some clinical symptoms of stroke (including: visual disturbances, visual field disturbances, dizziness and headache with a spinning sensation, nausea and vomiting, balance disorders, double vision, altered state of consciousness, febrile convulsions) may resemble the features of migraine with aura [44]. An epidemiological study suggests that migraine may constitute a risk factor for stroke, and moreover that stroke may occur during a migraine attack with aura [45]. In addition to this, hemiplegic migraine shows a significant similarity with acute stroke, however, the symptoms typically last less than an hour and appears to be self-limiting, often without sequelae [46]. Children suffering from arterial ischemic stroke are younger than those with migraine. Approximately 50% of patients experience arterial ischemic stroke under the age of 5, whilst median age for migraine oscillates around 13 years and 5 months. Aura will also appear less frequently in children under 8 in comparison with adolescents. In children with arterial ischemic stroke, the onset of symptoms is more sudden compared to patients suffering from migraine. Sensory and visual disturbances appear more frequently in children with migraine. On the other hand, signs of focal weakness, speech disorders, ataxia, seizures, inability to walk, hemiparesis and abnormal state of consciousness are significantly more common for children with arterial ischemic stroke. Differential assessment (based on magnetic resonance neuroimaging) in the emergency department is therefore crucial [44]. Differential diagnosis also includes epilepsy. Migraine and epilepsy share many similarities such as in their pathophysiology and clinical manifestations. Both of them are paroxysmal and therefore episodic disorders, and also may become chronic or recurrent. In particular, occipital lobe epilepsy can be misdiagnosed as migraine aura [47]. There are several similarities between photosensitive occipital epilepsy and migraine with aura: high prevalence in women, provocation of attacks by light stimuli and striped patterns, visual aura and autonomic disorders (such as pallor or vomiting). Electroencephalography should be performed to confirm a definitive diagnosis of epilepsy. Other features which may differentiate between the two conditions include visual symptoms (short in epilepsy or long in migraine) and severity of headache (much more severe in migraine than in epilepsy) [48]. Another disease entity that should be included in the differential diagnosis of migraine is a brain tumour. Headaches in patients with brain tumours (especially in case of craniopharyngioma) may resemble variants of migraine. Consequently, neuroimaging and conducting a thorough physical examination are crucial to correctly identify a brain tumor [49]. In conclusion, it is difficult to make a final diagnosis of migraine because neither objective tests nor specific markers exist for this condition [50]. Furthermore, the diagnostic process for migraine is particularly challenging in

paediatric patients because of their cognitive ability, limitations in vocabulary and difficulties in describing experienced symptoms [51].

Advances and future directions

Due to the high prevalence of migraine in the paediatric population globally, both the biopsychosocial approach and multidisciplinary therapeutic process should be undertaken. Crucial elements of that care constitute a mix of effective and early pharmacological treatment, education of patients and psychological support. The aim of therapy should be based not only on improvement of patient quality of life, but also on finding pain-coping strategies to better adapt to chronic disease [52]. Recent studies indicate that there are not observable differences in efficiency of amitriptyline, topiramate, and placebo in the treatment of paediatric migraine. While pharmacologic preventive treatment in children tends to be disappointing, psychological therapies (including cognitive-behavioural therapy) appear to be more effective in children than in adults [53]. CGRP - receptor antagonists may be a promising option in the future for both acute and preventive migraine treatment [30]. Monoclonal antibodies to CGRP or its receptor have had promising results in clinical trials for adults with migraine, and according to the conducted research, similar properties have been observed in adolescent subjects [54]. Moreover, the COVID-19 pandemic has also impacted children suffering from migraine. A remarkable reduction in migraine symptom intensity and frequency was noted during phases of COVID-19 lockdown. This emphasizes the importance of lifestyle modification (including reduction of school stress) in alleviating the course of migraine in children and adolescents [55,56].

Summary

Paediatric migraine is a unique disorder that tends to differ from migraine in adults [3]. The paediatric age group is particularly prone to psychological influences. Migraine therefore has a very significant impact across many spheres of lives of patients. It is related not only with physical pain, but may also lead to many long-term complications such as deterioration in quality of life, school difficulties or social disruption [20,21]. Despite the fact that approximately 1 in 10 children suffer from migraine, studies have found no significant effects of pharmacological prophylaxis [9,36], thus there is a need to provide more accurate preventive treatment in the future [37]. Advances in the understanding of migraine pathogenesis would allow a remarkable improvement in the effectiveness of medical care and could provide targeted therapies to approach even the earliest stages of migraine [57].

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