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Chronic Migraine in Adolescence

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Abstract

Chronic migraine (CM) is a clinically and epidemiologically important disease that generates considerable impairment to those affected by it, since there is evidence of higher incidence of depression, anxiety, and chronic pain in patients with this condition. It is characterized by the occurrence of headache for at least 8 migraine days in a month and at least 15 headache days in the same month. Despite the similarity in CM presented in adults, when in adolescents it has some particularities. Thus, the aim of this chapter was to conduct a literature review, using the databases: PubMed, SciELO, and LILACS, in addition to text books, explaining the definition, epidemiology, risk factors, diagnosis, pathophysiology, treatment, and prevention of CM in adolescent population.

Keywords: classic migraine, migraine with auras, epidemiology, adolescence, diagnosis

1. Introduction

Chronic migraine (CM) is defined as the occurrence of headache for at least 8 migraine days in a month and at least 15 headache days in the same month [1], being much less common and more debilitating than episodic migraine. Evidence indicates that migraine is a progressive disorder [2–4], and therefore, diagnosis and early management of episodic migraine are recommended, in order to avoid its chronicity, especially in adolescents; however, there is a failure in the accuracy of the diagnosis of CM in this population [5]. Migraine in this population can be misdiagnosed as sinusitis, attempted school skipping, and cerebral neoplasia, which may culminate in unnecessary testing [6].

2. Epidemiology

CM is a common disorder in children, and its incidence in adolescents presents a considerable increase [7]. Irrespective of age, the prevalence of chronic migraine is estimated at 1.5–2% in general population. On the other hand, its prevalence is 3% (from 3 to 7 years of age), 4–11% (from 7 to 11 years of age), and 8–23% (at 11 years of age), with a mean age of onset of 7.2 years for male and 10.9 years for female [8, 9]. Migraine is the 6th most disabling disease worldwide between the ages of 10 and 14 years and the 5th between the ages of 15 and 19 years [10]. In addition to the impact inflicted by pain itself, migraine generates serious consequences

in children's and adolescent's routine, since it is responsible for school absences, negatively affecting academic performance. It also has social impacts, since it hinders the child's interactions with his peers, and economic, due to the costs generated by the treatment [11]. Migraine has two-fold higher prevalence in females when compared to their peer male adolescents [12–17]. In women, the prevalence of migraine increases during adolescence, presenting a maximum prevalence at 30 years of age, decreasing sharply after menopause [12, 14, 17], since 50–60% of women report having migraine during their menstrual period [18]. In the American Migraine Prevalence and Prevention Study (AMPP), patients with CM presented with depression, anxiety, and chronic pain twice as much as patients with episodic migraine [17]. Abu-Arafeh et al., in 2010, estimated that the overall prevalence of migraine in children is 7.7% (9.7% in female and 6.0% in male), being more common in female after completing 11 years of age, in male before the age of 7, and being equal in both sexes between 7 and 11 years of age [19, 20]. In another study, WöberBingöl et al. reported general prevalence of migraine of 9.1% [21].

3. Risk factors

Among the risk factors for CM, the following are included:

- a. gender (female, once migraine has been associated with menorrhagia, dysmenorrhoea, and endometriosis [22]);
- b. age group;
- c. ethnicity: more specifically, white;
- d. genetic factors: family history of headache, mental disorders [5, 22, 23], anxiety, and depression [5, 23], as well as comorbidities, such as sleep disorders [5, 23] (sleep apnea syndrome and hypopnea, snoring, and insomnia [22]), obesity [23], epilepsy [24], hypertension, asthma, hypothyroidism, genitourinary disorders, musculoskeletal disorders, [22] and gastrointestinal disorders [22, 24];
- e. family and environmental factors: divorce [23], socioeconomic class [5, 23], and low level of education [5]; and
- f. other factors: pro-thrombotic factors [5] and pro-inflammatory factors [5, 23].

In addition to the factors mentioned above, others still under study may be related to the pathophysiology of CM and, therefore, represent risk factors such as traumatic brain injury, epilepsy, hemodialysis, and excessive use of symptomatic medications.

The existence of correlation between CM and traumatic brain injury was the subject of a systematic review study published by Sowell et al., in 2017, in which was sought to relate it to posttraumatic chronic headache (PTCH) in children and adolescents. In this study, it was observed that 7.6% of children with PTCH presented migraine [24], thus disclosing it to be a relatively common condition and that it should be considered.

Another factor that may be correlated with CM is epilepsy. Both migraine and epilepsy are considered neuronal hyperarousal-related diseases which can be partially prevented by antiepileptic drugs. According to the Center of Disease Control (CDC), 16.2% of adults with no history of epilepsy have severe headache or

migraine, while those with active epilepsy have 35.5% of prevalence [25]. Therefore, although the correlation between epilepsy and migraine has not been completely elucidated yet, there are strong indications for such an interdependence.

Regarding hemodialysis in pediatric and adolescent patients with chronic kidney disease, Davidovits and Eidlitz Markus, in a study published in the International Headache Society, concluded a three-fold higher prevalence of headache among patients in hemodialysis compared to those with chronic kidney disease without this treatment, the most commonly described type of headache being migraine. Furthermore, other variables were associated with headaches, such as anemia, hyperparathyroidism, and low glomerular filtration [26].

Notwithstanding, excessive symptomatic medication is also described in the literature as a risk factor for CM. With this in mind, Rojo et al. made a comparison between patients with CM with and without excessive medication use (analgesics, tryptans, ergotamine, and opioids). In the study, it was observed that individuals overusing symptomatic medication had the onset of migraine at a younger age, with a longer progression time before looking for a specialist, as well as a higher percentage of preventive prior treatment (mainly antidepressants), compared to those without excessive use of medication [5].

4. Diagnosis

Even though there are differences between the clinical findings of CM in the pediatric population and other age groups, due to the scarce evidence in relation to diagnostic methods aimed specifically at these patients, the International Classification of Headache Disorders, of Headache Classification Committee of the International Headache Society (IHS), 2018, is used, the same applied to the adult population [1, 5].

According to IHS, CM is characterized by occurrence of ≥ 8 days of migraine in a month and ≥ 15 headache days. Migraine attacks can be with and/or without aura [1]. In this case, migraine without aura is a headache lasting 4–72 h, which has at least two of the following characteristics: (1) unilateral location; (2) pulsatile character; (3) moderate to strong pain intensity; and (4) is exacerbated by routine physical activities and, during the headache, the patient has at least one of the following symptoms: (1) nausea and/or vomiting; (2) photophobia; and (3) phonophobia [1].

On the other hand, migraine with aura is a headache with the same characteristics mentioned above, plus one or more symptoms of fully reversible aura, and may be visual, sensory, speech and/or language, motor, brain stem, or retinal. Furthermore, crises should have at least three of the following characteristics: (1) at least one symptom of aura gradually spreads for more than 5 min; (2) two or more aura symptoms occur in succession; (3) each individual aura symptom lasts 5–60 min; (4) at least one symptom of aura is unilateral; (5) at least one symptom of aura is positive; and (6) aura is accompanied, or followed within 60 min, by headache [1].

Although the use of IHS criteria is recommended, the health professional should know the peculiarities of CM in adolescent population in order to complement the diagnosis. The characteristics of the headache tend to be more prominent in this group, since the brain is in the growth and development process. Furthermore, the duration of pain crises may be less than 1 h, contrary to the IHS criteria, which mentions a minimum duration of 2 h [1, 6, 27]. A direct relation between the patient's age and duration of crises is observed, being younger shorter the duration of the crisis [4]. An important information is that adolescents may present

nonpulsatile and bilateral pain, which may induce the misdiagnosis of tensional headache [2, 6, 27].

Approximately 10% of young people with migraine present aura, from visual, sensory, speech, or language disorders, motor, or brain stem changes, manifesting themselves as scotomas, paresthesias, dysphasias, hemiplegia, ataxia, or confusion. The suspicion of other diseases of the central nervous system should be listed through fever, nuchal stiffness, altered mental status, absence of family history of migraine, occipital or positional headaches, or headaches that constantly awaken the individual during sleep [28–30].

In adolescents, it is common for patients with migraine to have comorbidities such as epilepsy and atopy. The most common atopic disorders reported concomitantly with CM are seasonal rhinitis, conjunctivitis, and asthma, with correlation with positive family history. Regarding epilepsy, it is mainly associated with migraine with aura, which corroborates the role of depression of cortical propagation. Another hypothesis is that both, migraine and epilepsy, have the influence of canalopathies on their pathophysiology [30–32].

5. Pathophysiology

The mechanisms responsible for the occurrence of CM are not yet fully understood. Thus, the existing model to explain its pathophysiology still has gaps. It is accepted that migraine occurs by complex mechanisms involving activation and sensitization of trigeminal nociceptive pathways, especially its ophthalmic division, changes of the autonomic nervous system function, descending pain modulator system dysfunction, thalamic sensitization, and central sensitization due to the excessive use of medication in the acute treatment of pain crises.

It is noteworthy that the cortex of patients with migraine is hyperexcitable and abnormally sensitive to external stimuli. Due to triggering factors, the so-called cortical spreading depression (CSD) occurs, characterized by a slow propagation wave (2–6 mm/min) of sustained neuronal depolarization, which generates a transient peak of intense activity as it progresses in the tissue, followed by a long-term neural suppression. That is, there is a period of electrochemical hyperactivity followed by cortical inactivity, which results in the release of substances in the extracellular environment (ECE), such as K^+ and H^+ ions, nitric oxide, arachidonic acid, and prostaglandins [33–35]. Such a change in the ECE may activate or sensitize trigeminal afferences. The trigeminal ganglia, once stimulated, releases neuropeptides, causing inflammation of the dura mater. Cernuda-Morollón et al. demonstrate in their studies that interictal levels of calcitonin gene-related peptide (CGRP) and intestinal vasoactive peptide (IVP) are higher in CM [36, 37]. Thus, meningeal inflammation occurs, with vasodilation and endothelial dysfunction, resulting in plasma leakage and release of more inflammatory cytokines by mast cells. Thereby, neurogenic inflammation can lead to activation and sensitization of meningeal trigeminal afferences—a phenomenon known as peripheral sensitization [38–40].

A widely spread hypothesis is that increased peripheral nociceptive processing triggers increased activity of the descending pain modulation system, resulting in increased oxidative stress and consequent nociceptive modulation, further lowering the threshold for new pain crises. However, so far studies have not shown association between gene polymorphisms associated with oxidative stress and the occurrence of CM. On the other hand, repetitive painful stimuli on the trigeminal nerve cause activation of the pain modulating descending system in several portions, including the periaqueductal gray matter, showing that during migraine attacks, the

neurons of this region show increased activity, which may lead to oxidative stress and finally dysfunction of nociceptive modulation by such system [33, 41–43].

Thalamic modulation of trigeminal afferences appears to be related to the development of cutaneous allodynia in migraine, as sensitized thalamic neurons process nociceptive information from cranial meninges, along with sensory information from the scalp, skin, face, body, and limbs. Furthermore, the use of drugs that act modulating trigeminal afferences on the thalamus is effective in the preventive treatment of migraine attacks, such as topiramate, sodium valproate, and CGR66 receptor antagonists, corroborating the role of this structure in the chronicity of migraine [44–47].

The overuse of medications to relieve acute migraine may also lead to the chronicity of this condition, through the drug-mediated central sensitization mechanism, leading to increased susceptibility to cortical spreading depression. Central sensitization manifests clinically from increased pericranial sensitivity and allodynia [48–50].

Andersen et al. demonstrated in 2016 that during pain crises serum miRNA changes occur, and in patients with CM such changes persist the same in periods without pain. This implies the possibility of serum miRNA changes as a pathogenic feature of migraine. Thus, the study suggests that serum miRNA dosage is a potential biomarker of this disease [51].

According to Oakley et al., there is a possibility that obesity may be involved in the pathophysiology of migraine in the pediatric population. It is hypothesized that there is an overlap of the central and peripheral neural pathways responsible for the regulation of diet and those linked to the pathogenesis of migraine [33, 52]. Peterlin et al. demonstrated that several hypothalamic peptides, proteins, and neurotransmitters involved in the mechanisms of hunger also participate in the pathophysiology of migraine, such as serotonin, orexin, and adipokines. It is possible that the release of these substances, associated with the mechanism of diet and/or obesity states, may act as a trigger or corroborate the development of migraine. There is also the possibility that lifestyle and behavioral differences influence the relationship between migraine and obesity, such as differences in diet and physical exercise, or the lack of it [33, 53].

6. Treatment

6.1 General and supportive measures

The treatment of chronic migraine in adolescents aims not only to reduce frequency, duration, and intensity of the headache attacks, but also to reduce the consequences of this condition on the patient's quality of life, seeing as he or she is going through a process of growth and development. It also aims to treat comorbidities and reduce the social impact of the disease, such as school absences, school underachievement, and reduced peer interactions. Thus, the treatment should be developed from a multiprofessional perspective, with the help of pediatricians, neurologists and psychiatrists, psychologists, educators, and nutritionists, among others [54].

Firstly, family members should receive detailed information about the adolescent's diagnosis and ensure that the condition is not secondary to malignant diseases, in order to transmit confidence to the patient and their parents, thus contributing to treatment adherence [5].

Proper living habits are of paramount importance for treatment. However, the health professional should be careful to not excessively restrict the activities of young people, as this may lead to difficulties in adherence [55].

Sleep disorders are important comorbidities of chronic migraine. Therefore, regular sleep habits should be advocated in order to promote restful and restorative sleep. For this, the teenager can use some techniques, such as scheduling a daily bedtime, avoid using electronic media when in bed, avoid eating 4 h before bedtime, and avoid daytime naps. Still, sleep deprivation can be a triggering factor for pain crises, corroborating the importance of a well-slept night [56, 57].

Regarding food, it is important to prioritize regular meals, with the consumption of healthy foods and adequate hydration. Caffeine and tobacco should be avoided. The performance of physical activities should be encouraged, as it not only reduces the occurrence of crises, but also is able to assist in the treatment of depression and anxiety comorbidities, when present [58, 59].

Gelfand et al. emphasize that the patient should be alerted about the negative effects of overuse of medications, as it is one of the factors responsible for the chronicity of migraine, from the central sensitization mechanism, as previously explained about the pathophysiology [60].

Kroon Van Diest et al. [61], based on a randomized study, demonstrated the importance of Cognitive Behavioral Therapy (CBT) for adherence to pharmacological treatment and institution of lifestyle changes [62]. CBT aims, through interventions guided by a psychologist, to promote the patient's active learning in order to implement skills to deal with migraine and related conditions and situations to her. Thus, during the sessions, behavioral coping skills are worked out, such as problem-solving and thought restructuring, that is, the adolescent is urged to change their ideas, beliefs, and attitudes regarding his chronic condition [62]. CBT, in combination with amitriptyline, is suggested as a first-line treatment in the context of CM in adolescents [61].

6.2 Acute treatment

Regarding acute pharmacological treatment, that is, to relieve pain crises, nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans are used [28, 63, 64]. Among NSAIDs, the most used are ibuprofen and naproxen [28]. Evers et al. demonstrated that ibuprofen is better than placebo. There is no evidence regarding the efficacy of acetaminophen in adolescents [63, 65, 66].

In the adolescent population, the following triptans are indicated: sumatriptan, rizatriptan, zolmitriptan, and almotriptan. Studies indicate that such drugs are the most effective in relieving pain during acute crises in adolescents, with no statistically significant differences between them [63]. According to Derosier et al., the combination of naproxen and sumatriptan was superior to placebo when analyzing the permanence of analgesia after 2 h, with sumatriptan + naproxen sodium 10 mg + 60 mg (29%; $p = 0,003$), 30 mg + 180 mg (27%; $p = 0.003$), and 85 mg + 500 mg (24%; $p = 0.003$) versus placebo (10%) [67]. Among the side effects of this class, the most common are mild fatigue, paresthesia, dizziness, and taste disorders [28, 64].

In the case of long-term migraine or migratory status, that is, disabling crisis lasting more than 72 h, hospital treatment may be required for intravenous administration of prochlorperazine with ketorolac, which Brousseau showed that 57% of patients had pain reduction in 60 min [28, 68]. Dihydroergotamine (DHE) has been shown to be well tolerated and effective in acute treatment and is generally administered in hospital setting, and an association with metoclopramide or prochlorperazine is suggested, which is able to attenuate gastrointestinal side effects [28, 69]. Ayulo et al. suggested the use of intravenous lidocaine for the treatment of migratory status in adolescents, but further evidence is needed to ensure the long-term efficacy and safety of this medication [28, 70].

6.3 Preventive treatment

Prevention of chronic migraine attacks in adolescents remains limited [71, 72]. Newly developed therapies, including drugs, biologic products, and neuromodulation devices are safe and well tolerated in adults [73–80]. Studies in the pediatric population are still being developed [81]. Therefore, the current nonpediatric prevention will be presented.

Epidemiological studies suggest that approximately 38% of migraine patients require preventive therapy, however, only 3–13% currently use it [12]. The prevention of CM currently presents concrete evidence for the following drugs: onabotulinumtoxin A [82], topiramate [83, 84], and fremanezumab (TEV-48125) [85]. Other therapies, such as β -blockers and amitriptyline, are often used despite the lack of evidence, as they are not fully effective or poorly tolerated, which may culminate in low adherence rates [85]. However, a randomized study developed by Powers et al. demonstrated that amitriptyline, when combined with Cognitive Behavioral Therapy (CBT), reduces migraine disability and pain days by 1 month—adolescents receiving amitriptyline alone (group A) reduced the number of days with headache in 1 month of 6.8 days, while those who associated amitriptyline with CBT (group B) had a reduction of 11.5 days; headache disability as assessed by the Pediatric Migraine Disability Score (PedMIDAS) decreased by 52.7 points in group B versus 38.6 points in group A [62].

Currently, new forms of prevention have been proposed, based on the understanding of the pathophysiology of the disease. The calcitonin gene-related peptide (CGRP) has increased plasma concentration during a migraine attack [86–88]. Therefore, a human monoclonal antibody against the receptor of CGRP, named Galcanezumab, which was effective in preventing migraine when given at a dose of 150 mg twice a month, was developed in a study by Skljarevski et al. [89]. Treatment with self-administered injections of subcutaneous galcanezumab [90], subcutaneous fremanezumab [91], and enerumab [92] was associated with a reduction in the number of monthly days of migraine (5.6–6.5 days, 1.3–1.5 days, and 6.6 days, respectively).

Recent studies indicate that nonpharmacological strategies are effective in preventing CM, reducing the activation of peripheral nociceptive terminations. This can be accomplished by manipulation technique, increasing the range of motion and reducing the stiffness of the cervicothoracic spine. In the study by Gandolfi et al., patients undergoing this treatment had lower consumption of analgesics, NSAIDs, and triptans [93].

Guilbot et al. showed that *Tanacetum parthenium* L., magnesium, and coenzyme Q10, administered prophylactically for 3 months significantly reduced the number of monthly migraine days (4.9 ± 2.6 days) [94]. Silberstein et al. proposed the prevention of CM with noninvasive vagal stimulation, which presented better results in patients who underwent longer treatment times (6 months, in the study) [95].

7. Conclusion

CM in adolescents is a disease of clinical and epidemiological importance, since it can affect approximately a quarter of the pediatric population with an average of 11 years of age, being considered debilitating due to psychological, social, and economic repercussions.

This disorder has intrinsic and nonmodifiable (genetic and comorbidities) risk factors, as well as modifiable risk factors, such as behavioral and socioenvironmental variables, in addition to several other elements still under study that may contribute to the onset or that are correlated.

The diagnosis of migraine is made clinically according to the ICHD-3 criteria, taking into account the particularities of the adolescent population.

Pathophysiology, as well as risk factors and prevention, are still not completely elucidated items in CM. However, it is generally agreed that migraine occurs from complex mechanisms involving activation and sensitization of trigeminal nociceptives pathways, alteration of autonomic nervous system function, pain modulating descending system dysfunction, thalamic sensitization and further central sensitization due to the overuse of medicines in the acute treatment of pain crises.

Treatment, in turn, is multiprofessional and supported by both pharmacological and nonpharmacological measures. Nonpharmacological measures include guidance to parents and family members about the chronic condition, as well as sleep hygiene and adoption of good eating habits by the patient. In the case of drug measures, NSAIDs and triptans are the first option and, in case of migraine status, prochlorperazine associated with intravenous ketorolac added to recent evidence suggesting the use of intravenous lidocaine.

Finally, studies are still needed to fill the gaps present for the complete understanding of this complex and debilitating entity that is chronic migraine. Through a better understanding of the pathophysiological mechanisms responsible for the development of CM, as well as its risk factors, it will be possible to develop more effective prevention and treatment methods in adolescents.

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References

- [1] Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders. *Cephalalgia*. 2018;**38**(1):1-211
- [2] Lipton RB, Silberstein SD. Episodic and chronic migraine headache: Breaking down barriers to optimal treatment and prevention. *Headache*. 2015;**55**(2):103-122
- [3] Lipton RB, Pan J. Is migraine a progressive brain disease? *Journal of the American Medical Association*. 2004;**291**(4):493-494
- [4] Lipton RB, Bigal ME. Migraine: Epidemiology, impact, and risk factors for progression. *Headache*. 2005;**45**(1):3-13
- [5] Özge A, Yalın OÖ. Chronic migraine in children and adolescents. *Current Pain and Headache Reports*. 2016;**20**(2):1-7. DOI: 10.1007/s11916-016-0538-z
- [6] Gelfand AA. Migraine in young children. *Developmental Medicine and Child Neurology*. 2015;**57**(6):503
- [7] Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: A life-span study. *Cephalalgia*. 2010;**30**:1065-1072
- [8] Stewart WF, Linet MS, Celentano DD, Van Natta M, Siegler D. Age and sex-specific incidence rates of migraine with and without visual aura. *American Journal of Epidemiology*. 1991;**34**:1111-1120
- [9] Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. *Journal of the American Medical Association*. 1992;**267**:64-69
- [10] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;**388**:1545-1602
- [11] Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children: Association with school performance. *Neurology*. 2012;**79**:1881-1888
- [12] Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;**68**:343-349
- [13] Bigal ME, Liberman JN, Lipton RB. Age-dependent prevalence and clinical features of migraine. *Neurology*. 2006;**67**:246-251
- [14] Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia*. 2003;**23**:519-527
- [15] Ando N, Fujimoto S, Ishikawa T, et al. Prevalence and features of migraine in Japanese junior high school students aged 12-15 yr. *Brain & Development*. 2007;**29**:482-485
- [16] Zencir M, Ergin H, Sahiner T, et al. Epidemiology and symptomatology of migraine among school children: Denizli urban area in Turkey. *Headache*. 2004;**44**:780-785
- [17] Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: Data from the American migraine study II. *Headache*. 2001;**41**:646-657

- [18] Granella F, Sances G, Zanferrari C, Costa A, Martignoni E, Manzoni GC. Migraine without aura and reproductive life events: A clinical epidemiological study in 1300 women. *Headache*. 1993;**33**:385-389
- [19] Abu-Arafeh I, Razak S, Sivaraman B, et al. Prevalence of headache and migraine in children and adolescents: A systematic review of population-based studies. *Developmental Medicine and Child Neurology*. 2010;**52**(12):1088-1097
- [20] Mehta S. Study of various social and demographic variables associated with primary headache disorders in 500 school-going children of central India. *Journal of Pediatric Neurosciences*. 2015;**10**(1):13
- [21] Wöber-Bingöl Ç. Epidemiology of migraine and headache in children and adolescents. *Current Pain and Headache Reports*. 2013;**17**(6):1-11
- [22] Spierings ELH, Padamsee A. Menstrual-cycle and menstruation disorders in episodic vs chronic migraine: An exploratory study. *Pain Medicine*. 2015;**16**(7):1426-1432. DOI: 10.1111/pme.12788
- [23] Rojo E, Pedraza MI, Muñoz I, Mulero P, Ruiz M, de la Cruz C, et al. Diferencias entre migraña crónica con y sin uso excesivo de medicación: Experiencia en una serie hospitalaria de 434 pacientes. *Neurología*. 2015;**30**(3):153-157. DOI: 10.1016/j.nrl.2013.12.003
- [24] Sowell MK, Youssef PE. The comorbidity of migraine and epilepsy in children and adolescents. *Seminars in Pediatric Neurology*. 2016;**23**(1):8391. DOI: 10.1016/j.spen.2016.01.012
- [25] Shaw L, Morozova M, Abu-Arafeh I. Chronic post-traumatic headache in children and adolescents: Systematic review of prevalence and headache features. *Pain Management*. 2018;**8**(1):57-64. DOI: 10.2217/pmt-2017-0019
- [26] Davidovits M, Eidlitz Markus T. Headache in pediatric and adolescent patients with chronic kidney disease, with and without hemodialysis: A comparative cohort study. *Cephalalgia*. 2017;**38**(5):883-891. DOI: 10.1177/0333102417719235
- [27] Mariani R, Torriero R, Capuano A, et al. Clinical characteristics of primary headaches in children younger than 6 years. *Cephalalgia*. 2015;**35**:7-7
- [28] Slater SK, Powers SW, O'Brien HL. Migraine in children. *Current Opinion in Pediatrics*. 2018;**1**:775-778. DOI:10.1097/mop.0000000000000694
- [29] Lewis DW, Ashwal S, Dahl G, et al. Practice parameter: Evaluation of children and adolescents with recurrent headaches: Report of the quality standards Subcommittee of the American Academy of neurology and the practice Committee of the Child Neurology Society. *Neurology*. 2002;**59**:490-498
- [30] Newton RW. Childhood headache. *Archives of Disease in Childhood. Education and Practice Edition*. 2008;**93**:105
- [31] Özge A, Öksüz N, Ayta S, et al. Atopic disorders are more common in childhood migraine and correlated headache phenotype. *Pediatrics International*. 2014;**56**(6):868-872
- [32] Bellini B, Arruda M, Cescut A, et al. Headache and comorbidity in children and adolescents. *The Journal of Headache and Pain*. 2013;**14**(1):79
- [33] May A, Schulte LH. Chronic migraine: Risk factors, mechanisms and treatment. *Nature Reviews Neurology*. 2016;**12**(8):455-464. DOI: 10.1038/nrneurol.2016.93

- [34] Durham P, Papapetropoulos S. Biomarkers associated with migraine and their potential role in migraine management. *Headache: The Journal of Head and Face Pain*. 2013;**53**(8): 1262-1277. DOI: 10.1111/head.12174
- [35] Vecchia D, Pietrobon D. Migraine: A disorder of brain excitatory-inhibitory balance? *Trends in Neurosciences*. 2012;**35**:507-520
- [36] Cernuda-Morollón E et al. Increased VIP levels in peripheral blood outside migraine attacks as a potential biomarker of cranial parasympathetic activation in chronic migraine. *Cephalalgia*. 2015;**35**:310-316
- [37] Cernuda-Morollón E et al. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. *Neurology*. 2013;**81**:1191-1196
- [38] Waeber C, Moskowitz MA. Migraine as an inflammatory disorder. *Neurology*. 2005;**64**:S9-S15
- [39] Levy D. Migraine pain, meningeal inflammation, and mast cells. *Current Pain and Headache Reports*. 2009;**13**:237-240
- [40] Pietrobon D, Moskowitz MA. Pathophysiology of migraine. *Annual Review of Physiology*. 2013;**75**(1): 365-391. DOI: 10.1146/annurev-physiol-030212-183717
- [41] Schulte LH, Sprenger C, May A. Physiological brainstem mechanisms of trigeminal nociception: An fMRI study at 3T. *NeuroImage*. 2015;**124**:518-525
- [42] Youssef AM, Macefield VG, Henderson LA. Pain inhibits pain; human brainstem mechanisms. *NeuroImage*. 2016;**124**(Pt A):54-62
- [43] Gentile G et al. Lack of association between oxidative stress-related gene polymorphisms and chronic migraine in an Italian population. *Expert Review of Neurotherapeutics*. 2015;**15**:215-225
- [44] Burstein R et al. Thalamic sensitization transforms localized pain into widespread allodynia. *Annals of Neurology*. 2010;**68**:81-91
- [45] Andreou AP, Goadsby PJ. Topiramate in the treatment of migraine: A kainate (glutamate) receptor antagonist within the trigeminothalamic pathway. *Cephalalgia*. 2011;**31**:1343-1358
- [46] Andreou AP, Shields KG, Goadsby PJ. GABA and valproate modulate trigeminovascular nociceptive transmission in the thalamus. *Neurobiology of Disease*. 2010;**37**:314-323
- [47] Summ O, Charbit AR, Andreou AP, Goadsby PJ. Modulation of nociceptive transmission with calcitonin gene-related peptide receptor antagonists in the thalamus. *Brain*. 2010;**133**(9):2540-2548. DOI: 10.1093/brain/awq224
- [48] De Felice M et al. Triptan-induced latent sensitization: A possible basis for medication overuse headache. *Annals of Neurology*. 2010;**67**:325-337
- [49] Green AL et al. Increased susceptibility to cortical spreading depression in an animal model of medication-overuse headache. *Cephalalgia*. 2014;**34**:594-604
- [50] Becerra L et al. Triptans disrupt brain networks and promote stress-induced CSD-like responses in cortical and subcortical areas. *Journal of Neurophysiology*. 2016;**115**:208-217
- [51] Andersen HH, Duroux M, Gazerani P. Serum MicroRNA signatures in Migraineurs during attacks and in pain-free periods. *Molecular Neurobiology*. 2015;**53**(3):1494-1500. DOI: 10.1007/s12035-015-9106-5

- [52] Oakley CB, Scher AI, Recober A, Peterlin BL. Headache and obesity in the pediatric population. *Current Pain and Headache Reports*. 2014;**18**(5):1-12. DOI: 10.1007/s11916-014-0416-5
- [53] Peterlin BL, Tietjen GE, Gower BA, et al. Ictal adiponectin levels in episodic migraineurs: A randomized pilot trial. *Headache*. 2013;**53**:474-490
- [54] De Angelis V, Cherubini F, Nigrelli G, Erbuto D, Martelletti P. Multimodal therapy in the management of MOH: 3 year experience. *The Journal of Headache and Pain*. 2015;**16**:135
- [55] Sieberg CB, Huguet A, von Baeyer CL, Seshia S. Psychological interventions for headache in children and adolescents. *The Canadian Journal of Neurological Sciences*. 2012;**39**(01):26-34
- [56] Guidetti V, Dosi C, Bruni O. The relationship between sleep and headache in children: Implications for treatment. *Cephalalgia*. 2014;**34**(10):767-776
- [57] Calhoun AH, Ford S. Behavioral sleep modification may revert transformed migraine to episodic migraine. *Headache*. 2007;**478**(11):787-811
- [58] Straube A, Heinen F, Ebinger F, von Kries R. Headache in school children: Prevalence and risk factors. *Deutsches Ärzteblatt International*. 2013;**6**(57):811-818
- [59] Verotti A, Di Fonzo A, Penta L, Agostinelli S, Parisi P. Obesity and headache/migraine: The importance of weight reduction through lifestyle modifications. *BioMed Research International*. 2014;**2014**:420858
- [60] Gelfand AA, Goadsby PJ. Medication overuse in children and adolescents. *Current Pain and Headache Reports*. 2014;**18**(7):1-6
- [61] Kroon Van Diest AM, Ramsey RR, Kashikar-Zuck S, Slater S, Hommel K, Kroner JW, et al. Treatment adherence in child and adolescent chronic migraine patients. *The Clinical Journal of Pain*. 2017;**33**(10):892-898. DOI: 10.1097/ajp.0000000000000481
- [62] 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. *Journal of the American Medical Association*. 2013;**310**(24):2622-2630
- [63] Richer L, Billingham L, Linsdell MA, Russell K, Vandermeer B, Crumley ET, et al. Drugs for the acute treatment of migraine in children and adolescents. *Paediatrics & Child Health*. 2017;**22**(8):454-458. DOI: 10.1093/pch/pxx170
- [64] Patniyot IR, Gelfand AA. Acute treatment therapies for pediatric migraine: A qualitative systematic review. *Headache*. 2016;**56**:49-70
- [65] Evers S, Rahmann A, Kraemer C, Kurlmann G, Debus O, Husstedt IW, et al. Treatment of childhood migraine attacks with oral zolmitriptan and ibuprofen. *Neurology*. 2006;**67**(3):497-499. DOI: 10.1212/01.wnl.0000231138.18629.d5
- [66] Lewis DW, Kellstein D, Dahl G, Burke B, Frank LM, Toor S, et al. Children's ibuprofen suspension for the acute treatment of pediatric migraine. *Headache*. 2002;**42**(8):780-786. DOI: 10.1046/j.1526-4610.2002.02180.x
- [67] Derosier FJ, Lewis D, Hershey AD, Winner PK, Pearlman E, Rothner AD, et al. Randomized trial of sumatriptan and naproxen sodium combination in adolescent migraine. *Pediatrics*. 2012;**129**(6):e1411-e1420. DOI: 10.1542/peds.2011-2455

- [68] Brousseau DC, Duffy SJ, Anderson AC, Linakis JG. Treatment of pediatric migraine headaches: A randomized, double-blind trial of prochlorperizine versus ketorolac. *Annals of Emergency Medicine*. 2004;**42**:256-262
- [69] Kabbouche MA, Powers SW, Hershey AD, et al. Inpatient treatment of status migraine with dihydroergotamine in children and adolescents. *Headache*. 2009;**49**:106-109
- [70] Ayulo MA Jr, Philips KE, Tripathi S. Safety and efficacy of IV Lidocaine in the treatment of children and adolescents with status migraine. *Pediatric Critical Care Medicine*. 2018;**19**:755-759
- [71] Lewis D, Ashwal S, Hershey A, et al. Practice parameter: Pharmacological treatment of migraine headache in children and adolescents: Report of the American Academy of Neurology quality standards subcommittee and the practice Committee of the Child Neurology Society. *Neurology*. 2004;**63**:2215-2224
- [72] Jackson JL. Pediatric migraine headache—Still searching for effective treatments. *The New England Journal of Medicine*. 2017;**376**:169-170
- [73] Silberstein SD et al. Fremanezumab for the preventive treatment of chronic migraine. *The New England Journal of Medicine*. 2017;**377**:2113-2122
- [74] Misra UK, Kalita J, Bhoi SK. High frequency repetitive transcranial magnetic stimulation (rTMS) is effective in migraine prophylaxis: An open labeled study. *Neurological Research*. 2012;**34**:547-551
- [75] Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. *The New England Journal of Medicine*. 2017;**377**:2123-2132
- [76] Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: 10 month 2019 the randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;**91**:e2211-e2221
- [77] Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. *Cephalalgia*. 2019;**39**:3-14
- [78] Martelletti P, Barbanti P, Grazi L, et al. Consistent effects of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: Additional findings from the randomized, sham-controlled, double-blind PRESTO trial. *The Journal of Headache and Pain*. 2018;**19**:101
- [79] Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. *Neurology*. 2018;**91**:e2222-e2232
- [80] Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. *Cephalalgia*. 2016;**36**:887-898
- [81] Hornik CP, Gelfand AA, Szperka CL, Pezzuto T, Utevsky A, Kessel S, et al. Development of a prospective real-world data clinical registry of children and adolescents with migraine. *Headache: The Journal of Head and Face Pain*. 2019;**0**:2-9. DOI: 10.1111/head.13714
- [82] Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache*. 2010;**50**:921-936

- [83] Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: A randomized, placebo-controlled trial of quality of life and other efficacy measures. *Headache*. 2009;**49**:1153-1162
- [84] Silberstein SD, Lipton RB, Dodick DW, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. *Headache*. 2007;**47**:170-180
- [85] Bigal ME, Edvinsson L, Rapoport AM, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: A multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet Neurology*. 2015;**14**:1091-1100
- [86] Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Annals of Neurology*. 1990;**28**(2):183-187
- [87] Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: Studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Annals of Neurology*. 1993;**33**(1):48-56
- [88] Juhasz G, Zsombok T, Modos EA, et al. NO-induced migraine attack: Strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release. *Pain*. 2003;**106**(3):461-470
- [89] Skljarevski V, Oakes TM, Zhang Q, Ferguson MB, Martinez J, Camporeale A, et al. Effect of different doses of galcanezumab vs placebo for episodic migraine prevention. *JAMA Neurology*. 2018;**75**(2):187. DOI: 10.1001/jamaneurol.2017.3859
- [90] Camporeale A, Kudrow D, Sides R, Wang S, Van Dycke A, Selzler KJ, et al. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. *BMC Neurology*. 2018;**18**(1):1-10. DOI: 10.1186/s12883-018-1193-2
- [91] Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab compared with placebo for prevention of episodic migraine. *Journal of the American Medical Association*. 2018;**319**(19):1999. DOI: 10.1001/jama.2018.4853
- [92] Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: A randomised, double-blind, placebo-controlled phase 2 trial. *The Lancet Neurology*. 2017;**16**(6):425-434. DOI: 10.1016/s1474-4422(17)30083-2
- [93] Gandolfi M, Marchioretto F, Turrina A, Dimitrova E, Geroin C, Valè N. Does myofascial and trigger point treatment reduce pain and analgesic intake in patients undergoing OnabotulinumtoxinA injection due to chronic intractable migraine? A pilot, single-blind randomized controlled trial. *European Journal of Physical and Rehabilitation Medicine*. 2017;**54**(1):1-12
- [94] Guilbot A, Bangratz M, Ait Abdallah S, Lucas C. A combination of coenzyme Q10, feverfew and magnesium for migraine prophylaxis: A prospective observational study. *BMC Complementary and Alternative Medicine*. 2017;**17**(1):1-6. DOI: 10.1186/s12906-017-1933-7
- [95] Silberstein SD, Calhoun AH, Lipton RB, Grosberg BM, Cady RK, Dorlas S, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation. *Neurology*. 2016;**87**(5):529-538. DOI: 10.1212/wnl.0000000000002918