

Chronic Migraine in Children and Adolescents

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Abstract Chronic migraine is defined as having more than 15 headache days in a month, half of these showing migraine features, for at least 3 months. It is a chronic painful syndrome with aspects such as psychiatric comorbid, decreased quality of life, and environmental and intrinsic psychological factors that make face-to-face treatment difficult. Children and adolescent migraine differ from adults as a result of growing brain and evolving disorder. In this paper, we will emphasize the definition, diagnosis, epidemiology, burden of life, and management of chronic migraine in children and adolescent.

Keywords Chronic migraine · Children · Diagnosis · Management · Burden

Introduction

Most of our knowledge about chronic migraine (CM) in children and adolescent emerges from adult experience. CM is defined in the third edition of the International Classification of Headache Disorders (ICHD-3 beta) as the presence of headaches on 15 days or more in a month, at least 8 days showing the migraine phenotype (ICHD-3), for more than 3 months

[1]. However, CM is much less common than episodic migraine in clinical settings, and it is substantially more debilitating with a greater negative effect on the quality of life and challenging for practitioners [2, 3]. Despite the substantial personal and societal consequences, the diagnostic criteria of CM are still evolving [4]. ICHD-3 beta published in 2013 has comprehensively described primary chronic headache disorders, such as CM, chronic tension-type headache, new daily persistent headache, and chronic hemicrania continua [1]. Herein, childhood chronic migraine is not mentioned. Since childhood migraine features and demographics have huge differences depending on growing age and gender, CM in children is also far from standard adult features of CM.

CM is an underdiagnosed and unrecognized disorder [5]. Attacks may interfere with the predictability of normal life activities; affect the ability to work, to perform routine course, school activities, and to maintain functional social relations; and decrease the quality of life. CM patients constitute the most debilitated subgroup of the migraine population, so they may represent a clinically distinct group [6]. In children and adolescents, chronic migraine has differences from many aspects from diagnostic symptoms to management protocols. In general medical applications, from malignancy to neurodegenerative diseases, the current thumb rule is early diagnosis to prevent advanced destruction, and this is also accurate for CM. It is well known that chronicity is closely related with disease duration and frequent attacks, in addition to genetic background and comorbidities. And, there is a body of evidence mentioning that migraine is a progressive disorder at least for some patients [4, 7, 8]. Thus, the hypothesis is if we could appropriately diagnose and manage episodic migraineurs, we could prevent some patients to become chronic migraineurs, especially in children and adolescents. Unfortunately, there is a lack of accurate evidence for diagnosis and management of chronic migraine in children [9].

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In this paper, we aimed to discuss the current knowledge about chronic migraine in children and adolescents under the following four topics: epidemiology, diagnostic sets, differential diagnosis, and management.

Epidemiology

In 2010, the Global Burden of Disease reported migraine as one of the most disabling disorders. In the migraine population, CM patient is the most debilitated subgroup [10••]. After the recognition of CM burden worldwide, scientists investigated the scope of the problem with epidemiological studies. Herein, children and adolescent migraine epidemiological studies frequently followed the adult ones. Even in this group, lastly and less investigated group of children migraine is CM epidemiological studies. There are only a few population-based studies investigating children and adolescent CM population, and this leads to limited knowledge about the burden of CM, and thus, limited effective evidence-based management of patients [11•, 12–14].

A prevalence rate of approximately 2–3 % for CM has been estimated for adult population [15–17]. In the American Migraine Prevalence and Prevention (AMPP) study, patients with CM had two times higher developing depression, anxiety, and chronic pain than those with episodic migraine (EM) [17]. Cutaneous allodynia, anxiety, disability, and depression are frequently considered as predictors of chronification in adult population [4, 18]. Epidemiology of migraine in children and adolescents is reviewed at two large meta-analyses. Abu-Arafeh et al. at 2010 estimated that the overall prevalence of migraine for children is 7.7 %, which is the average of 9.7 % for females and 6.0 % for males. They report that headache is more common in female children after 11 years of age. Migraine is reported more common in male children under 7 years of age and equally prevalent for both genders between 7 and 11 years of age [19••, 20]. In another article, Wöber-

Bingöl et al. reported overall prevalence of migraine as 9.1 %, higher [10••] than reported by Abu-Arafeh et al.

We investigated the prevalence of CM in children and adolescents in Mersin, a city in Turkey [11•]. The studies revealed that 10.4 % of the study population was diagnosed with migraine, 1.7 % with CM, and 8.6 % with EM. CM frequency increased exponentially with ages and doubled at the age of 12. Identified risk factors for chronification were age, gender, and father and sibling headache history. Lipton et al. investigated prevalence and burden of chronic migraine in adolescents with 8883 episodic headaches and 890 chronic headaches [11•, 12]. They reported a prevalence rate of CM 0.79 % excluding medication overuse and 1.75 % including medication overuse [12]. In another study, Arruda et al. investigated on children younger than 12 years of age in Brazil and reported overall prevalence of chronic daily headache 1.68 % in this population [13]. In spite of heterogeneous sample and methodology, these studies conclude that prevalence of CM in children and adolescent could be regarded as roughly 1.5–1.8 %; CM prevalence is increasing with age and especially for girls after adolescent. Family history of chronic headache seems to be an additive risk factor for chronification at this age group. Table 1 refers to summarized data of mentioned epidemiological data.

Definition and Diagnosis

Clinical phenotype of CM in children and adolescents can be mentioned as follows: headache characteristics of CM in children are prominently different from adults, and this is generally explained by evolution of migraine at growing brain with the some prominent differences before or after puberty. Duration of headache attacks in children could be less than 1 h. Duration of headache is mentioned at ICHD-3 beta as 2–72 h, but there are studies reporting that the minimum duration could be 1 h or may be even less [23]. Duration of headache

Table 1 Reported prevalence studies of chronic migraine in children and adolescents

Author/year	Country	Population	Age/year	Criteria	Migraine %	CM%	CDH	EM %	Chronicity-related factors
Özge A/2013 [11•]	Turkey	5562	8–16	ICHD-2	10.4	1.7	–	8.6	Age, gender, and family headache history
Lipton/2011 [12]	USA	9773	12–17	ICHD-2	–	0.79 ^a	3.5	–	–
Wang/2009 [21]	Taiwan	103	12–14	ICHD-2	–	–	–	–	Headache frequency, MIDAS score, and baseline CDH
Arruda/2010 [13]	Brazil	1994	<12	ICHD-2	3.76	0.8	1.86	–	Age and race
Galinski/2015 [22]	France	142	<20	–	8 %	–	–	–	Age ≥ 12 years at the time of presentation
Krogh/2015 [14]	Norway	493	12–18	ICHD-3 beta	23	0.8	–	–	–

^a Lipton et al. reported low CM prevalence, but when adolescents with medication overuse were included, estimated prevalence was 1.75 %

seems particularly related with age. In a study, it was shown that half of the children younger than 6 years of age reports attack duration shorter than 30 min [24].

It should be underlined that headaches frequently have non-throbbing and bilateral location in children and adolescents up to third decades of life. In children, behavior is more important than words, meaning that observations of relatives, parents, and teachers could be more valuable than a report. These two criteria could cause a misdiagnosis of chronic tension-type headache. In fact, for some authors [25], tension-type headache in children is not a different entity from migraine but could be regarded as a different presentation of the same spectrum of primary headache in children. There is evidence supporting this idea. Many tension-type headaches may turn into typical migraine; moreover, there is evidence of same neurophysiological abnormalities shared with patients [25–31]. The supposed best items of migraine characteristics are moderate to severe intensity and pain aggravation by physical activity. The most specific features separating migraine from tension-type headache are improvement after sleeping; the presence of nausea and vomiting; worsening with physical activity; and photophobia, phonophobia, or osmophobia. As children pass through adolescence, their migraines begin to resemble migraine in adults [32, 33]. A problem with small-aged children is that they could not exactly define their symptoms. In this age group, drawing a picture of headache is very informative in many aspects for clinician (Fig. 1).

Clinician should be aware that associated autonomic symptoms are more frequent at migraine population resembling sinusitis headache but it is also an important clinical feature of childhood migraine apart from trigeminal autonomic cephalalgias [34]. The other specific features of childhood migraine are comorbidities with atopic disorders and epilepsy. Some clinical setting data show the important comorbidity of atopic disorders in children and adolescents migraine. These comorbidity changes are partially correlated with the headache presenting time and the headache phenotype. Puberty has an important effect on the atopic disorder comorbidity of migrainous children. The most common reported atopic disorders are seasonal rhinitis, conjunctivitis, and asthma with an important ratio of positive family history [35].

Migraine and epilepsy comorbidities are well known, particularly in children and adolescence. The most obvious association is epilepsy and migraine with aura (MwA). This supports the role of cortical spreading depression of the comorbidity. Another hypothesis which supports the correlation of the mentioned diseases is channelopathy. There are no researches to support the specific association of chronic migraine and epilepsy, should they be associated at all [36–38].

On the other hand, there are accumulated evidence to show a possible relation between headache and obesity. Population-based studies revealed that body mass index is correlated with migraine attack frequency, chronicity, and functional

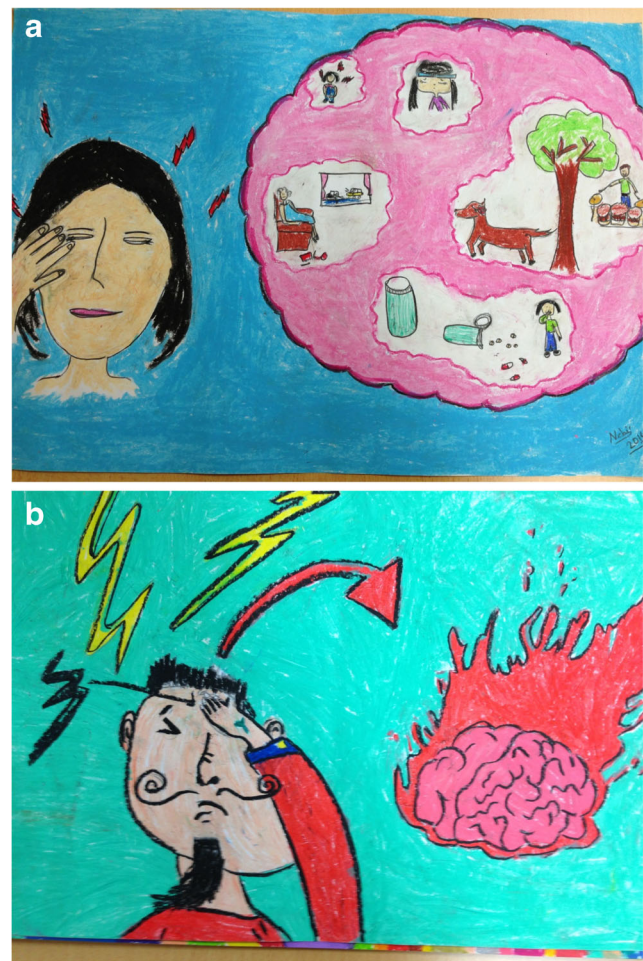


Fig. 1 a A 10-year-old girl drawn by her CM with her triggers. b An 8-year-old boy drawn by his severe CM

disability [39–41]. In a recent review, it is reported that there is need for new studies to explain pathophysiology of obesity and chronic headache in children [42].

CM Versus Chronic Daily Headache

There is no detailed evidence suggesting that primary chronic daily headache (CDH) in children is different from adults. Since episodic migraine phenotype is significantly different for children, it is expected to have clinical differences for CDH. Migraine diagnostic features including throbbing, unilateral headache, and associated symptoms are subtle in children; the same is also true for CM in adults and children. This result leads to a prominent confusion to differentiate tension-type headache (TTH) and migraine from each other at clinical and research settings. CDH group covers, CM, chronic tension type headache (CTTH), new daily persistent headache (NDPH), medication overuse headache (MOH), and hemicrania continua. Hemicrania continua are very rare in children and are not mentioned in this article. The other forms

of CDH in children do not have precisely different features to distinguish. In our study which covered episodic and chronic migraine subjects, we did not observe significant difference in clinical picture of patients [11•]. Currently, we propose clinicians to use ICHD-3 beta criteria to differentiate CDH in children and adolescents, but we need to be aware that TTH or CM diagnosis does not have exact lines in this age group, and in the following years, diagnosis could shift from TTH to CM or vice versa.

Burden of Disease

Chronic migraine has prominent impact on a child's activities, such as school absences, reduction in school success, and decreased home and friend interactions. In a very recent study, authors report that at least 8 days are lost because of headache in general recurrent headache population, and they report that the most bothersome features are the intensity and the duration of headache. Since these features are the characteristics of migraine, school absence for CM is expected to be more prominent [43]. Pediatric migraine disability assessment (PedMIDAS) is a validated questionnaire that assesses school, home, and playing disability by reports of children [44]. The questionnaire consists of the following topics: school absence, poor functioning at school, disruption of home, and social activities for a period of 3 months. It is based to MIDAS questionnaires developed for adults. Recent studies criticize PedMIDAS from the perspective of lower detection of after school activities [45]. They address its potential defects covering non-school days; long holidays could not be evaluated by questionnaire. Critical point at the follow-up is that clinician should not decide according to one instrument and therapy should be prepared and sustained with the experience of a headache expert. The pediatric quality of Life Inventory, version 4.0 (PedsQL 4.0), is a validated questionnaire developed to examine children from age 2 to 18 years. PedsQL 4.0 is used for various chronic diseases. Ferracini et al. reported that there are physical and school disabilities in children, and they show emotional and social aspects of the chronic disease [46]. Even though migraine-related burden of life is documented for children, CM-related burden of life is not well documented at this age group. Masruha et al. reported that CM is strongly associated with social anxiety disorder when compared with episodic migraine and healthy controls [47].

Childhood migraine cases, particularly girls, psychiatric comorbidity, medication overuse, onset after 13 years of age, and patients who have had headache for more than 2 years should be carefully followed [48]. CDH in children is a complex, difficult to treat syndrome partially due to its comorbidity with psychopathology (Table 2) [49]. Anxiety and depression are major comorbid conditions, and also, nearly one third

Table 2 Main cofactors of CM in children and adolescents

Genetic
Family history of headache
Mental illness
Anxiety and depression
School
Grades
Teachers
Friends
Environment
Diet
Weight
Physical activity
Sleep
Comorbidities
Atopic disorders
Epilepsy
Irritable bowel syndrome
Psychiatric disorders
Family
Divorce
Substance abuse
Blended family
Family resources

of the CDH patients concurrently show at least one psychiatric disorder criterion [50, 51].

Management of CM in Children and Adolescents

The aims of management of CM in children are not only to decrease headache days/month, intensity, and duration of attacks but also to cover the negative effect on the quality of life on a developing body. Another aim is to recover comorbid psychiatric and preparative environmental conditions, prevent school absences, and to improve chronic headache-related impairment of quality of life. By reason of multiple aims at therapy, the management protocols should be multidisciplinary [52, 53].

Non-Pharmacologic Treatments

Management of CM begins after detailed clinical examination with multimodalities as first step, completed with required investigations, reassuring of parents that CM is a primary headache syndrome and is not due to brain tumor or other life-threatening disorders. The confidence of family and child or adolescent is mandatory at first step to ensure that everybody is on the same page. Information and education process

should include teachers and school counselors in addition to parents. The management and adjustments should not interfere with the subject's daily life and success [54].

The role of lifestyle should not be overemphasized, and clinician should be careful not to restrict and cause major changes on the lifestyle of the children. Some important points of lifestyle have been summarized as follows:

Sleep A regular restorative sleep habit could improve getting rid of the negativities of CM. Guidetti et al. observed that the most frequent comorbidity of migraine is sleep disorder in children followed by anxiety disorder. Moreover, they emphasize that cooccurrence of sleep and headache disorder is also related with chronification and treatment failure [53]. It is known that sleep deprivation is one of the common triggering factors at migraine; moreover, sleep is associated with relief of migraine attack at most of the patients. Although headache management needs an individualized management, there are some general interventions proposed to use at migraine [55]. We recommend (1) to schedule bedtime and to avoid watching television, listening music, playing with electronic devices, or reading in bed; (2) do not eat at least 4 h before bedtime; and (3) to avoid daytime naps [53, 55, 56].

Eating Habits Although there are many foods reported as possible triggers of migraine attacks for CM, through chronification processes, many of the triggering factors diminish. Skipping meal is the most important point which should be emphasized, and regular meals and appropriate hydration should be provided. Caffeine overuse and smoking should be avoided [57].

Physical Exercise Regular exercise is established to lessen headache in chronic daily headache, and it could also be helpful for developing self-confidence and diminishing psychiatric comorbidities such as depression and anxiety [58]. Although obesity and chronic headache comorbidity is recognized, the etiology of this relationship is still unclear. Therapeutic lifestyle modifications and maintenance of regular physical activity are important strategies to prevent adult obesity and to cope with CM [59].

Medication Overuse It is common in children and adolescents than adults, particularly among those with chronic migraine. The available drugs are commonly used un-prescribed non-specific analgesics, paracetamol, and ibuprofen, but narcotic analgesic or triptan overuse is also common [60]. Barbiturate-containing drugs and opioids are seriously problematic and should be avoided. This situation not only is a predictor of chronification but also a covariant of changing clinical phenotype of CM [60, 61]. To start, preventive therapy is principal approach in helping children and adolescent, precluding the overuse of medications. Greater occipital nerve

injections and IV dihydroergotamine could have a role in bridge therapy [60].

Pharmacologic Treatments

Acute Attack Treatment The aims of acute attack treatment are to treat attacks rapidly, restoration of functional ability, to prevent medication overuse, and self-care with minimal side effects. Medications should be taken shortly after onset of migraine headache to optimize the effect, even though scientific evidence supporting this recommendation is lacking. The medication should be available to the patients also at school. The effectiveness and safety of many of drugs in children and adolescents are not well studied. However, in children, short duration of the attacks and minimum activation time for maximum effect of the attack drugs have to be considered. Main comments of the migraine attack studies in children and adolescents are summarized as follows:

- At short time (1 h), acetaminophen tended to be slightly more effective (39 % of children relieved) than ibuprofen (37 % of children relieved), but 2 h after administration, ibuprofen was more effective (68 vs. 54 %) supported by randomized controlled trials (RCTs). Acetyl salicylic acid (ASA) should be avoided because of the risk of Reye's syndrome in early childhood.
- Sumatriptan nasal spray was superior to placebo and was well tolerated. No serious adverse events occurred with taste disturbance as the most common one. However, it should be caution in children diagnosed as MWA and hypotension.
- There are supportive scientific data about rizatriptan, zolmitriptan, and almotriptan approved by The Food Drug Administration and Europe in children over 12 years old. However, we need more supportive long-term comparative studies.
- Based on the available literature, no differences in effect were found between the different compounds reported in attack management. There is a lack of studies addressing the question of treatment in the emergency department of children with migraine, especially MWA. Future studies should focus on finding the best first-line agent for mild to moderate attacks in the emergency department. Furthermore, treatment to decrease the recurrence of migraine attack and the need for rescue medications after discharge from the emergency department should also be carefully evaluated [62•, 63, 64, 65•].

Preventive Treatment General principles related to the goals of migraine preventive therapies in children and adolescents are to (1) reduce attack frequency, severity, and duration; (2)

improve responsiveness to treatment of acute attacks; (3) improve migraine-associated features and their negative effect on daily living activities; and (4) improve function, reduce disability, and improve the patient's quality of life [62••, 65••]. There is no drug approved for specific treatment of CM in children and adolescents. The non-pharmacological options should always be supported with drug regimens. Drugs always started a monotherapy with a tapering dose taking account for comorbidities of the patients and potential side effect of the drugs in a growing body. In children and adolescent age groups, amitriptyline or propranolol is the most known pharmacological option and there is limited evidence with other potential preventive treatment options (Table 3) [62••, 63]. In a recent meta-analysis, authors evaluate the effects of pharmacologic interventions [64]. They summarize 24 publications of 22 RCTs; only one agent propranolol was reported to be more effective than placebo to prevent migraine. Topiramate, valproic acid, clonidine, trazodon, and magnesium failed to be effective in migraineous children or adolescents. Valproic acid and topiramate reported that significantly adverse effects resulted to discontinuation of treatment. Clinical decision giver should be aware of drug side effects and carefully estimate the balance of benefits and harms of drugs especially in a developing body. Valproic acid, ciproheptadin, and amitriptyline are related with weight gain, and conversely, topiramate is related with weight loss. Valproic acid and topiramate are also conducting toward decreased attention period of children and adolescents, possibly

ending up with a decreased academic performance. Despite the lack of RCTs, these agents are commonly prescribed in CM children. The rationale to use these agents are comorbidities, such as valproic acid for a generalized epileptic child or using topiramate for an obese adolescent. Similarly, there are no RCTs that evaluated selective serotonin reuptake inhibitors for CM. But, these agents could be very useful to treat comorbid psychiatric conditions with multidisciplinary approach [62••, 63, 64, 65••]. They have to give a through time period (at least 4–6 months), and both comorbidities and side effects of the drug have to be taken into consideration [62••].

Botulinum Toxin A (Bont-A) Treatment Bont-A treatment is used for preventive treatment of chronic migraine that is unresponsive to other prophylactic treatment alternatives and approved by Food and Drug Administration (FDA), in USA, for the treatment of CM in adults. The approving of Bont-A for CM is based to double-blind, placebo-controlled studies (PREEMPT) [66]. But, there are lack of similar strong evidence for children and adolescent population. Kabbouche et al. reported Bont-A treatment effect on their study [67]. They report better results for headache frequency, duration, and intensity parameters without serious side effects. We emphasize Bont-A treatment for above 12 years of age, unresponsive to other treatments, significantly lots of QOL children. There is a strong need for placebo-controlled, double-blind studies to state exact effects of treatment.

Table 3 Evidence related with abortive treatment of migraine attacks. Revised from Lewis 2004 AAN

practice parameter (64).
Ibuprofen
10 mg/kg (4–16 y) Class I
7.5 mg/kg (6–12 y) Class I
Acetaminophen (15 mg/kg) (4–16 y) Class I
Sumatriptan
Nasal 20 mg (6–14 y) Class I
Oral 50,100 mg (8–16 y) Class I
Subcutaneous 3, 6 mg (6–16 y) Class IV
Rizatriptan 5 mg (12–17 y) Class I
Zolmitriptan 2.5, 5 mg (12–17 y) Class IV
Amitriptyline 10–75 mg/day
Divalproex sodium, sodium valproate 250–1000 mg/day
Flunarizine 5–10 mg/day
Metoprolol 25–200 mg/day
Propranolol 80–240 mg/day
Timolol 10 mg/day
Topiramate 50–200 mg
Botulinum toxin treatment
Great occipital nerve blockage with anaesthetics

Greater Occipital Nerve Injections in CM

The effect of greater occipital nerve (GON) injections with local anesthetics like lidocaine or provacaine together with or without steroids is supportive with respect to the data in recent years [68, 69]. In a new study, Gelfand et al. investigated the effects of GON injections for chronic pediatric headache patients including chronic headache syndromes [70]. They injected into the most tender side and used methylprednisolone acetate plus lidocaine. The effects of injections started at 5 days and 62 % of CM patients benefited from injections, superiorly to NPDH headache patients. They report that the efficacy of GON injection should be investigated with double-blinded, placebo-controlled studies. GON injections also could be used as off-label bridge therapy for patients under prophylactic treatments [70].

Conclusions

Chronic migraine is a common condition in children and adolescents with the full aspects of a chronic pain syndrome. After establishment of ICHD 3-beta, CM diagnostic criteria are evolved and included medication

overuse headache. However, we need more data about epidemiology, risk factors, and changing clinical pictures of CM in children and adolescents with growing body. On the other hand, the establishment and elimination of these modifiable environmental factors could be helpful in the prevention of CM. In clinical practice, management of CM is mainly preventive medicine partly supported by bridge or attack management including some limited interventions. Finally, we need to more future studies, investigating clinical characteristics of CM in children and adolescents, chronicity-related factors, and effective preventive drugs.

Compliance with Ethical Standards

Conflict of Interest Aynur Özge and Osman Özgür Yalın declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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