Primary Headache in Children and Adolescents: From Pathophysiology to Diagnosis and Treatment

Abstract
Primary headaches are common disorders among children and adolescents; tension type headaches (TTH) and migraine being the most frequent types.

This paper reviews the literature and summarizes the knowledge regarding the underlying pathophysiological mechanisms that cause headaches, mainly TTH and migraine, discusses the diagnostic criteria for primary headaches, and the different modalities for management of pain in children and adolescents.

It is well accepted, that the pain experience holds bio-psychosocial components to it, therefore treatment strategies should be tailored according to the patient’s age, headache diagnosis, family structure, culture and beliefs, and according to the disability the headache imposes on the patient’s daily living. A multidisciplinary treatment, that includes counseling, education and reassurance combined with pharmacological and non-pharmacological treatment, was found to be the effective strategy to alleviate the symptoms of primary headaches in children and adolescents.

Keywords: Primary headaches; Migraine; Tension type headache; Children; Adolescents

Introduction
Headaches are common in children and adolescents, the most common pain complaint when seeking medical advice [1]. Primary headaches are one of the most common disorders of childhood, with migraine and tension type headache (TTH) being the most frequent ones [1]. In spite of their prevalence, there is paucity of knowledge regarding the underlying pathophysiological mechanisms that cause headaches, regarding the unique aspects of pediatric and adolescent headaches and in regards to their evolution into headache disorders in adults. Most of our current knowledge is driven from extrapolations from studies that were conducted with adult patients. Children and adolescents are very different than adults in regards to their rapid growth, significant development, and psychological changes that happen during this time of life. Thus, findings from studies conducted on adults need to be validated for the pediatric age group. This article will discuss primary headache that do not require any laboratory or imaging evaluation. In some instances, though, when the treating physician suspects a non-primary origin of headache—further investigation may be warrant [2]. If any of the following features are present, one may consider evaluation: new onset of headache, changes in a stable headache pattern, headache that changes with posture, first onset of headache prior to 3 y of age, headache awakening the patient at night. In case of any abnormal neurological symptoms or signs, trauma, or a history of malignancy—further investigation is recommended [2].

This article will review the current knowledge about primary headaches in children and adolescents, their pathophysiology, diagnosis, and different modalities for treatment.

Headache diagnosis
The current standard for diagnosis of headaches is the International Classification of Headache Disorders 3rd edition (beta version) [3]. As the criteria are designed to be a tool by which scientific studies of headaches can be advanced, it holds standardized criteria that balance specificity and sensitivity for
universally diagnosing headache disorders. There is no date yet on the new criteria and their application to children.

**Migraine syndromes**

**Diagnosis:** The older version of the ICHD-II criteria [4] had been studied for the diagnosis of pediatric and adolescent migraine [5, 6]. They were found to capture only 61.9% of the young subjects that clinically had migraine when the adult criteria were applied. When footnotes that were specifically aimed for diagnosis of migraine in children were included, the percent of diagnosis increased to 73.9%. The primary factor responsible for this increase was the note relating to the duration of pain that was required for diagnosis [5]. These studies demonstrated that while the ICHD-II was shown to be very useful in adults, there were still gaps in its applicability for diagnosing pediatric headaches. The greatest gaps were not clinical, as most of the subjects were still clinically recognized as having migraine, but rather in the research field. Therefore, studies looking at the etiology, epidemiology and treatment of migraine syndromes in the pediatric age group may have missed many clinical presentations due to inaccurate interpretation of childhood migraine syndromes [7].

A different approach was suggested for the diagnosis of pediatric migraine presenting in the Emergency Department (ER)-by the Irma’s ED criteria [8]. These criteria consist of:

- Headache episodes of 1-72 h presenting with 4 of the 6 following criteria:
  1. Moderate to severe episode of impaired daily activities
  2. Focal localization of headache
  3. Pulsatile description
  4. Nausea or vomiting or abdominal pain
  5. Photophobia or phonophobia or avoidance of light and noise
  6. Symptoms increasing with activity or resolving by rest.

These criteria are stated to be more sensitive and easy to use than the ICHD-II, with annotation for pediatric criteria, especially when used in the emergency department setting [8].

**Pathophysiology**

Although primary headaches’ diagnosis is still made only by anamnestic data and neurological examination [9], during the past decade neurophysiologic techniques and neuroimaging studies were utilized to achieve greater understanding of the complexity of primary headaches’ pathophysiology. It is believed, that in the near future these modalities will assist in making the diagnosis itself.

Migraine has been long considered to be a disease of the head vasculature structures. However, more evidence has accumulated about the involvement of the cerebral cortex, and about its role in the cascade of events which trigger the migraine attacks [10]. This led to the use of the following neurophysiologic studies: Visual evoked potentials (VEP), somatosensory evoked potentials (SEP), and auditory-cortex potentials (MMN). Migraine was found to be associated with abnormal central information processing and with altered cerebral cortex excitability [11]. It has been postulated that in patients suffering from migraine, the cortex’ lack of habituation activates the trigemino-vascular system, thus leading to the painful attack [12]. Surprisingly, the phenomenon of reduced VEP habituation, largely confirmed in adults [13], has not been demonstrated in children with migraine [14]. Among the primary sensory cortices, the most frequently studied in children was the visual area. An early visual evoked potential (VEP) study showed higher amplitude to flash stimulation in children with migraine than in healthy subjects [15]. Another phenomenon that was described in pediatric migraine was a shortened SEP recovery cycle. This abnormal recovery cycle was shown to be partially restored by prophylactic treatment with topiramate [16]. Since topiramate acts in migraine by blocking voltage-dependent sodium channels [17], it has been postulated that there might be a linkage in pediatric migranous patients between the abnormal SEP recovery cycle and a high intracellular Na\(^+\) concentration. To note, that to the best of our knowledge the phenomenon of shortened SEP recovery cycle has not been investigated in adult with migraine thus far.

Recent studies have shown that some memory, attention, and visuomotor abnormalities are present in migraine patients [18, 19]; therefore a few electrophysiological studies regarding cognitive function in children with migraine were conducted [19]. Valeriani et al conducted a study that indicated a reduced MMN habituation in both children with migraine and children with tension type headache (TTH) [20]. MMN is a cognitive response elicited by physically deviant auditory stimuli occurring among frequent (“standard”) stimuli. Its reduced habituation in those children supported the hypothesis, that in the pediatric age group the abnormal brain excitability represents a common background for both migraine and TTH. Thus authors have suggested that migraine and TTH in childhood are not distinct entities, but rather two aspects of the same spectrum of benign headache [21]. This hypothesis was also backed up by clinical studies, showing that during childhood many episodes that were diagnosed as TTHs may with time turn into typical migraines [22, 23]. The lack of clear difference between Migraine and TTH in children and adolescents continued to gain support from studies using Contingent Negative Variation (CNV). CNV reflects the preparation of a signaled movement and the simultaneous anticipatory attention for the imperative stimulus [24]. It includes two components: An early component, representing the activation of the anterior cingulate cortex, the supplementary motor area and the prefrontal cortex, and a late component, distributed in the centro-parietal area [25]. While in healthy subjects the amplitude of the early CNV component decreases with age and its habituation increases, in patients with migraine the amplitude of the early CNV remains stable at different ages and its habituation decreases with age [26]. These results have been interpreted as an expression of lack of the visual system maturation during childhood and adolescence. This means, that the psychophysiological mechanisms of spatial attention in children with primary headache are more similar to those of adults than to those of healthy children [26]. The distinct neurophysiologic differentiation between migraine and TTH which is clearly demonstrated in adulthood does not seem to apply to the pediatric age. In adults, the most typical
neurophysiologic abnormality found in migraineurs is the evoked potentials habituation deficit, but it does not occur in TTH patients. In children and adolescents suffering from headache, a reduced EP habituation was either not found [14], or was shown in both-children with TTH and children with migraine [20]. It has been shown that in children with TTH, the headache type may often turn into migraine and vice versa [22, 23]. Hence, it is conceivable that in the pediatric age group there might be a common pathophysiological background for both TTH and migraine, thus the diagnostic differentiation between these two types of primary headaches is more difficult, and maybe less useful than it is for adults [27].

Tension-Type Headaches

Tension-type headaches (TTH) are a heterogeneous syndrome, which is diagnosed mainly by the absence of features that are found in other headache types, such as migraine. Thus, TTH are featureless headaches that are characterized by nothing more than “a pain in the head” [28]. The term “tension-type” was determined by the first Classification Committee of the International Headache Society in 1988 [29] to provide a new diagnosis that underlined the uncertain pathogenesis, yet indicated that some kind of mental or muscular tension might have a causative role in its evolution. Because the exact pathogenesis of TTH remained unknown, the term tension-type was maintained in the 3rd edition (beta version) of the International Classification of Headache Disorders as well [3]. TTH, which is commonly shorted to “tension headache”, is the most common form of headache in all age groups [30]. In spite of its high prevalence it receives much less attention than other types of headache from health authorities, clinical researchers, or industrial pharmacologists. One of the reasons for that may be the fact that most people with infrequent TTH do not consult a doctor for pain relief. They usually manage it themselves using over-the-counter analgesics [31]. However, chronic TTH, defined as headache that occurs on 15 days or more per month, is a major health problem with significant educational and socioeconomic effects. To date there are no clear guidelines for the diagnosis of TTH, therefore the definition relies exclusively on clinical symptoms, which are less distinct than the symptoms of migraine. Because of the lack of disease-specific features, TTH may mimic several secondary headaches (those which are caused by another disorder), thus making it more challenging for the clinician to decide whether or not the symptoms require further investigation, to rule out a secondary cause [31].

Pathophysiology of TTH

It is still in debate whether the pain in TTH originates from myofascial tissues or from central mechanisms in the brain. Progress in research in this field is challenging because of the difficulty in obtaining a homogeneous population of patients, owing to the lack of specificity of clinical features and diagnostic criteria. The various pathophysiological abnormalities of TTH, and the differences between TTH types, led to the proposal of a model of TTH as a working hypothesis [32, 33]. One of the proposed pathophysiological mechanisms for TTH was that it may be a result of the interaction between changes in the descending control of second-order trigeminal brainstem nociceptors, and interrelated peripheral changes, such as myofascial pain sensitivity and strain in the pericranial muscles [32]. An acute episode of TTH can occur in people who are otherwise perfectly healthy. It can be triggered by a variety of insults such as physical stress, psychological stress, or a combination of both, and by a working position that is not properly ergonomic. In such cases, increased nociception from strained muscles might be the primary cause for the headache, (possibly favored by a central temporary change in pain control due to stress) [32]. Increased emotions are thought to trigger TTH by several mechanisms: They cause an increase in muscle tone through the limbic system and, at the same time, reduce the tone of the endogenous antinociceptive system [31]. When the headache episodes become more frequent, central changes become increasingly important. Long-term sensitization of nociceptive neurons, in combination with a decreased activity of the antinociceptive system may cause chronic headache. These central changes are important both in frequent episodic TTH and in chronic TTH; however the relative importance of peripheral and central factors may change between patients. It was assumed, that genetic factors have a role in modulating psychological and central changes that lead to CTTH, while environmental factors have the key role in the development of episodic TTH [31].

Chronic Daily Headache

The term “chronic daily headache” (CDH) was first used by Mathew et al. to describe headaches occurring almost every day in a subgroup of adults. In almost 80% of these patients, there had been a transformation from episodic headaches to daily headaches [34]. The commonly used definition for all subtypes of CDH was established by Welch and requires the following components [35]:

- A headache episode occurring for 15 or more days per month for 3 or more consecutive months.
- A daily headache episode that lasts either more or less than 4 h.

An association between psychosocial stressors, psychiatric disorders (especially anxiety and mood disorders), and CDH was described by Seshia et al. [36]. This association may be partially explained by the concept of the “limbic augmented pain syndrome” [37]. This model relays on the kindling mechanism to explain how exposure to a noxious stimulus may under certain conditions lead to a sensitized cortico-limbic state. Thus, a history of exposure to psychological trauma may configure the neurobiologic substrate for later-amplified pathologic responses [37]. A study conducted in Taiwan examined the prevalence of psychiatric disorders in adolescents that were diagnosed with CDH. It included 121 adolescents with CDH, aged 12 to 14. Different types of psychiatric disorders were found in almost half of these patients: Over one third of the subjects had anxiety disorders, depressive disorders were found in one third, and one fifth of the subjects had a high score on “current” suicidal scales [38]. The prevalence of all the mentioned psychiatric disorders was substantially higher than in age-matched control patients. To note, that the risk for CDH and psychiatric comorbidity was highest in girls, and in children who had a background of migraine, especially with aura [38]. The observations regarding an association between
CDH and psychiatric disorders have been confirmed in another clinic-based study [36], and in a study looking at unexplained chronic pain [39]. The strongest association with CDH was found to be with anxiety and mood disorders (specifically depression). Other disorders mentioned were anorexia, somatoform and factitious disorders. The recognition of a psychiatric comorbidity is crucial to successful management and pain control of CDH [36].

Overweight and obesity were also found to be in association with CDH. Overweight girls, but not boys, were found to have an almost fourfold prevalence of headaches when compared with normal-weight girls [40]. As the prevalence of obesity in children and adolescents is increasing rapidly worldwide-it is reasonable to assume that the prevalence of headaches, that were shown to be associated with it, will increase as well. Obesity may affect self-esteem and obese children may be subject to teasing, therefore it is a potential psychological stressor that might make obese children prone to develop CDH [40]. Another contributing factor for the development of CDH is medication overuse and substance abuse [41].

**Age as a Factor in Primary Headaches**

Primary recurrent headaches are common in all age groups, but the effect of age on their prevalence may be dramatic [42]. Taking migraine as an example: Prior to puberty, the prevalence of migraine is slightly higher in boys than in girls; during early adolescence, the incidence and prevalence of migraine increases more rapidly in girls than in boys [43]. The overall prevalence increases throughout childhood and early adulthood until approximately 40 years of age, declining thereafter [44]. The impact of age is also seen for other primary headaches, such as tension-type headaches [45] and chronic daily headaches [46]. The age factor also plays a role in the phenotype and clinical presentation of primary headaches. For migraine, it has been demonstrated that the ratio between probable migraine and migraine decreases with age, suggesting that full-blown migraine is more common during adolescence and adulthood than in childhood [47]. Similarly, the presentation of CDH differs considerably between adolescents and adults; chronic TTH and new daily persistent headaches are relatively more common in adolescents, while chronic migraine (CM) is more prevalent in adults. Furthermore, adolescents with CDH are less likely to overuse acute medications than adults [46]. Looking at the differences in the prevalence and the clinical phenotypes of primary headaches over the life span may shed light on different mechanisms that may hold an effect on the evolution of headache syndromes. Determinants of evolution of primary headaches should be studied in the younger age groups (children and adolescents), whereas long-term consequences of primary headaches should be studied by conducting research that involves an elderly population.

**Treatment Principles for Primary Headache Syndromes**

Treatment strategies for primary headaches vary according to patient’s age, family structure, culture and beliefs, headache diagnosis, and according to the disability the headache imposes on the patient’s daily living [48]. A multidisciplinary treatment approach was found to be an effective strategy for children and adolescents: It was shown to improve multiple outcome variants, including frequency and severity of headache, and school days missed because of headache [47].

**Counseling and Education**

Due to the variety of bio-psychosocial components in the evolution of primary headache, education of the family and patient regarding the diagnosis, its natural course, and the different possible treatment modalities is of great importance. Educating patients about how different triggers, emotional and psychological ones, influence a headache attack, and how managing triggers can reduce the number of headache attacks, increases the patients’ internal locus of control, meaning the sense the headache episode could be under their control [49]. Reassurance about no underlying imminent disease may also be of value in case the patient and the family show great concerns about it.

**Pharmacological Treatment**

When recommending pharmacological treatment one must take into consideration the age and gender of the patient, headache diagnosis, comorbidities, and side effects of the pharmacological agent [48].

**Treatment for an acute pain episode**

An acute episode of migraine deserves a slightly different treatment approach than an acute episode of TTH. In the case of acute migraine the aim of treatment is to alleviate pain so that the patient will be able to return to normal functioning within 1-2 h without the risk of relapse [50]. The pain caused by an acute episode of migraine is relatively easy to control, as long as it is treated early in the course of the attack, even by OTC’s such as ibuprofen and acetaminophen that were shown to be effective for that purpose in children [51]. In a more severe episode the use of triptans is fairly common and was shown to be safe in the pediatric age group [52]. Yet, only almotriptan (6.25 mg, 12.5 mg) has been approved for the use of children by the Food and Drug Administration (FDA) [53].

In the case of an acute episode of TTH a more gradual strategy is appropriate, as the patients’ activity is usually not interrupted and pain intensity is usually not severe [54]. In case of repeated, prolonged, or severe episodes of both types of primary headaches, the use of prophylactic treatment should be considered.

**Pharmacological prophylaxis**

Life style changes are recommended for young people with migraine, who are struggling with the burden of their headaches: sleep hygiene, regular exercise, and a balanced diet [55]. For those who have demonstrated persistent disability (as assessed by either Pediatric Migraine Disability Assessment Score- PedMIDAS-or by persistent school absence) in spite of lifestyle modification, pharmaco-prophylaxis should be employed [54]. The cases of repeated, prolonged, or severe episodes of both types of primary headaches, where the use of prophylactic treatment should be considered, are: Frequent migraine episodes (>1 to 2 per week, or >3 to 4 per month), patients experiencing headache-related disability that interferes with daily activities such as school
attendance, and daily routines (e.g. Pediatric Migraine Disability Assessment Score PedMIDAS >30) [56], and patients that are prone to extremely intensive, prolonged (>48 h), hemiplegic, or basilar-type migraine or to severe aura. Prophylaxis should also be considered if acute treatment options are either ineffective, or not tolerated, contraindicated, or regularly overused [48]. For patients suffering from frequent episodic TTH and moreover for those suffering from chronic TTH, prophylactic treatment should be considered as well [41, 54].

Topiramate at 100 mg a day has been shown to be effective in reducing the burden of headaches when compared to placebo [57]. Other studies using amitriptyline [55] and propranolol [58] showed conflicting results. Cyproheptadine has been studied as well, showing positive effects, yet its use is often limited by the troubling side effects of somnolence and weight gain it may hold [59]. A large-scale, prospective, double-blinded, placebo-controlled study, aimed to compare the effectiveness and safety of amitriptyline, topiramate, and placebo for prevention of childhood and adolescent migraine is ongoing, and its results will hopefully assist the clinician when prescribing pharmacoprophylaxis for that purpose [60].

**Adjunctive pharmacological therapy**

Many of the children and adolescents diagnosed with migraine will present during an acute pain episode with nausea and vomiting, in part due to gastroparesis [61]. This phenomenon might delay the absorption of the anti-pain medication and therefore usage of promotility and anti-emetic medication might be beneficial in such patients. Prochlorperazine, chlorpromazine, promethazine, and metoclopramide have all been shown to relieve nausea in acute migraine episodes, while also showing some therapeutic effect for the migraine itself [61]. In addition, anxiety was found to be a common comorbidity in patients with migraine, either primary, as a pre-existing comorbidity, or secondary, due to the severe pain experienced by the patient during the acute pain episode. An anxiolytic agent was shown to be beneficial in patients who experience anxiety during an acute migraine attack. It does not address the underlying pathophysiology of migraine, but it can reduce the suffering during the attack [61].

**Non pharmacological treatments**

Pharmacological as well as non-pharmacological treatments for primary headaches require counseling, on-going education and reassurance for the patient, family, and often the peer group. Non-pharmacological treatments include relaxation techniques, biofeedback training, different psychotherapeutic approaches such as cognitive-behavioral therapy, strategies relating to daily living activities, family relationships, school, friends and leisure time activities, or combinations of these treatments. Data supporting the effectiveness of these measures in children and adolescents are less clear-cut than in adults [48], yet a recent Cochrane review of psychological therapies for the management of chronic and recurrent pain in children and adolescents that different modalities of psychological interventions delivered face-to-face were effective in reducing pain intensity and disability for children and adolescents with headache, and that the therapeutic gains appeared to be maintained during follow-up [62].

**Relaxation techniques**

Relaxation techniques are common non-pharmacological treatments used for different symptoms in which anxiety and elevated muscle tone seem to play a role in triggering the symptom. These are relatively easy to administer, cheap and well tolerated by patients [63]. The two more commonly used techniques are progressive muscle relaxation and autogenic training. The effectiveness of both relaxation strategies has been proven in several studies and meta-analyses for pain relief in headache syndromes [64]. The effect of relaxation techniques may be mediated by a direct impact on the underlying cause of headache, i.e., increased muscle tone, or it may hold an indirect effect by reducing anxiety [65]. Despite many studies that were conducted on relaxation techniques, their specific underlying neurophysiologic effect on headaches remains uncertain. One of the hypotheses is that habituation to repetitive stimulation is typically reduced in patients with migraine, and relaxation increases habituation toward normal values [66]. Relaxation may also reduce cortical arousal and excitability [67], which may result in reduced information processing of pain-modulating subcortical areas [68]. However, these possible neurophysiological mechanisms have still to be proven. Muscle relaxation techniques require repeated training which includes contraction and relaxation of different muscle groups. There are specific instructions for practicing relaxation in the younger age group, depending on age, compliance, and motivation for change of the child and his or her family [64]. It was shown, that self-administered versus therapist-administered interventions had similar effects on pain reduction [63]. A relatively recent small pilot study has shown beneficial effects of a combination of relaxation and biofeedback techniques in children [69].

**Biofeedback techniques**

Biofeedback is the process of gaining awareness of autonomic physiological functions using instruments that provide information on the activity of those same systems, e.g. brainwaves, muscle tone, skin conductance, heart rate, respiratory rate, etc. The goal of biofeedback treatment is to be able to manipulate those functions at will, either towards relaxation (to decrease anxiety, for instance) or for excitation (to improve achievements in short term missions such as sports). To achieve this goal, the physiological function has to be fed back visually or acoustically to the subject so it would be perceived in a conscious manner [70]. Biofeedback can be used in the context of behavioral interventions to increase autoregulatory competence; hence, the effect of successful biofeedback training may be similar to the effect of cognitive restructuring [70]. According to a recent meta analyses, evidence levels for the positive effect of biofeedback in the treatment of migraine or tension-type headache in children and adolescents are high [70]. Another meta-analysis indicated that biofeedback was highly efficient in management of chronic pain in children and adolescents, and comparable with pharmacologic prophylaxis [63]. It was shown to be effective in episodic as well as chronic headaches in the pediatric age group,
with the concurrent use of an SSRI being a positive predictive factor for a positive response. The use of prophylactic medication was associated with no favorable response to biofeedback treatment [71].

**Headache diary writing**

One of the common and well-studied behavioral strategies for the management of pain is the use of a “headache diary”. Recording a diary by itself was shown to reduce headache frequency in children and adolescents [72]. A slightly different version of this behavioral strategy is the use of a more detailed diary, that records daily activities, patterns of sleep, workload in school, and the proportion of time spent on “work” versus leisure time. This type of diary could be useful for the estimation of stress load and examination of the impact it holds on pain episodes [48]. Recording the type and amount of analgesic taken by the patient is also of great importance, mainly in order to prevent medication overuse, which may cause augmentation of pain. This phenomenon, of medication overuse headache, is well documented in adults, but might occur in children as well, therefore should be addressed [73].

**Operant-behavioral treatment**

The operant model focuses on pain behaviors as a major component of the pain problem, and postulates that they are subject to environmental contingencies [74]. It acknowledges that suffering may be distinct from pain, yet contribute to it, and that pain may be triggered by anticipation of threat to one’s self or identity [75]. The effectiveness of operant-behavioral treatment has been studied in relation to chronic pain, and in particular 3 therapeutic techniques were shown to be effective: graded activity, activity pacing, and time-contingent medication management [76]. In this therapeutic approach, patients learn to deal with pain instrumentally, or via operant conditioning; i.e., they learn to approach and deal with potentially pain-triggering situations instead of avoiding them [77].

**Cognitive-behavioral treatment**

Over the past three decades, cognitive-behavioral therapy (CBT) has become a first-line psychosocial treatment for individuals with chronic pain. The goals of CBT in pain syndromes are to reduce pain and psychological stress related to it, and to improve the physical state and functioning of the patient [78]. The means by which these goals are achieved are by helping the patient recognize and correct maladaptive thoughts and beliefs, reduce maladaptive behaviors and increase adaptive ones, and increase self- efficacy for pain management. CBT enables the patient to come in contact with the symptoms that accompany painful episodes/chronic pain, especially with negative emotions that may arise, like anxiety and depression [79]. In all patients with recurrent or chronic pain episodes, but more so in children and adolescents, CBT aims to prevent or reduce headache episodes, and to modify the cognitive-emotional and cognitive-behavioral processes that influence pain [72]. Psychological treatments (mostly CBT) delivered face-to-face were found to be effective in reducing pain intensity and disability for children and adolescents with headaches, and these therapeutic gains appeared to be maintained at follow-up [80]. CBT is often delivered in conjunction with pharmacotherapy. A randomized control trial looking at adolescents with chronic migraine that were all treated pharmacologically with amitriptyline indicated that those patients who were also treated with CBT had greater reductions in days with headache and migraine-related disability compared to those treated with headache education plus amitriptyline [81]. Many studies have shown a beneficial effect of CBT on headaches and its psychological comorbidity (mainly depression and anxiety) [72, 78], yet many young people do not receive psychological treatments for chronic pain due to barriers such as a shortage of providers, expense, and geographic distance from treatment centres [82]. A Cochrane review aiming to assess the effectiveness of psychological therapies delivered remotely and comparing them to waiting-list, treatment-as-usual, or active control for the management of chronic pain in children and adolescent is being held [80]. Its’ conclusions may shed light on the preferred non-pharmacological modality for treating these young patients.

**Internet-based self-help behavioral techniques**

With the widespread use of the internet by young people, many internet-based self-help strategies were developed, aiming to relieve challenging emotions/experiences/situations in children and adolescents’ lives. Among them are self-help techniques for relieving the burden of recurrent headaches. A randomized controlled trial compared 3 self-help internet based techniques: CBT, applied relaxation and education intervention. All techniques showed significant reduction in headache frequency, and duration, but not in headache intensity, and health-related quality of life. CBT showed the highest reduction in headache frequency [83]. A randomized trial of a web-based intervention to improve migraine self-management and coping for adults with migraine showed promising results in increased headache self-efficacy, increased use of relaxation, increased use of social support, decreased pain catastrophizing, decreased depression, and decreased stress [84]. A pilot study assessing the feasibility and preliminary effectiveness of an Internet-delivered CBT intervention for adolescents with chronic headache did not demonstrate a beneficial effect for the CBT group. Yet, both groups reported high levels of engagement with the web program and reported satisfaction with the intervention [85]. More prospective well-controlled studies are required to reliably assess the effectiveness of different web-based interventions.

**Nutraceuticals**

Many patients and many families of children and adolescents who have a chronic condition turn to Nutraceuticals, which they believe is “a more natural way” than pharmacotherapy for treating their condition [86]. The word “nutraceuticals” is a portmanteau of the words “nutrition” and “pharmaceutical”, and the term is applied to products that range from isolated nutrients, dietary supplements and herbal products, specific diets and processed foods. Alone and in combination, magnesium, riboflavin, coenzyme Q10, and the herbal extracts of butterbur, feverfew, and ginkolide B have all been suggested as preventative for migraine [87]. It is postulated
that intracellular magnesium may be decreased in migraineurs, resulting in a decreased migraine threshold through a number of interdependent pathways. Riboflavin is a precursor for flavin compounds necessary for mitochondrial oxidation, which may be impaired in migraineurs [87]. Coenzyme Q10 is necessary for electron transport, exhibits anti-inflammatory properties, and has been shown to be protective against glutamate toxicity, which is thought to play a key role in the pathogenesis of migraine. Butterbur extract (Petasites) was shown to have antispasmodic, anti-inflammatory, and vasodilator properties [88, 89]. However, in spite of the growing basis of knowledge about nutraceuticals and their possible therapeutic effects, studies involving pediatric patients looking at the use of a single or combination of nutraceuticals in the treatment of pediatric headache are still missing.

Summary
Primary headaches are common among children and adolescents; Migraine and TTH being the most common types. In spite of their high prevalence, most of our knowledge concerning pathophysiology, diagnostic criteria and treatment modalities is driven from extrapolations from studies that were conducted with adult patients. These extrapolations should be implemented cautiously to the pediatric age group as there are significant differences between children and adults regarding the development and maturation of neuronal circuits, the psychosocial development and status, and therefore the pathophysiology and prevalence of different headache types. These differences noted in regards to the type and presentation of headaches between children and adolescents to adults may shed light on the progression of childhood headache disorder into adulthood.

In this review we have summarized the current literature regarding primary headaches in children and adolescents, mostly migraine, tension type headache and chronic daily headache. Their diagnoses, pathophysiology, and different treatment modalities were discussed. The recommended treatment strategies, pharmacological and non-pharmacological alike, should be tailored according to patients’ age, family structure, culture and beliefs, headache diagnosis, and according to the disability the headache imposes on the patient’s daily living [48]. Having reviewed the literature it seems safe to suggest, that the recommended approach to treatment of primary headache in children and adolescents is the multidisciplinary approach. This approach is comprised of education, ongoing support, behavioral techniques, and medications as needed, and takes into consideration the stage of development the young patient is at. The multidisciplinary approach was shown to improve multiple outcome variables such as frequency and severity of headache, school days missed, stress levels, anxiety etc. Further studies regarding application of new neuroimaging techniques will most likely improve our understanding of the pathophysiology of primary headache, and our ability to accurately diagnose the young patients. Further studies on different modalities of treatment, alone and in combination, will assist physicians to
better serve their young patients, who struggle with the common
and burdening phenomenon of headache.

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