Pediatric Headache

Evaluation Through Treatment for the General Provider

Christopher B. Oakley
Editor

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I would like to dedicate this pediatric headache manuscript to Donald W. Lewis, M.D. (May 15, 1951–February 17, 2012). I was fortunate enough to meet Don when I was an undergraduate student at the University of Virginia. After our initial meeting, he quickly became someone I looked up to as my advisor and mentor; but in reality he was so much more to me over the years. Throughout the next 12–13 years, Don was my teacher, my mentor and advisor, a future colleague, and most importantly a friend. It was Don who instilled my love and passion for not just pediatric neurology, but more specifically, pediatric headache by making headache medicine fun and exciting. Don taught me how to be a caring clinician who put his patients and their families first; he taught me how to care for the whole patient, rather than just for their specific presenting concern; he taught me the power of education; he taught me how to be a mentor and advisor; and he taught me how to be a leader. It is because of Don that I continue to strive to be not only the best pediatric headache clinician I can be but

also a leader in the field of headache medicine, all the while working to also be the best medical educator, advisor, and mentor that I can be to those around me. While Don is no longer with us, his memory and legacy will never be forgotten, and I cannot thank him enough for all that he did for me and all that he continues to do for me. Thank you Don, thank you for being my mentor, my teacher, and my friend—you will never be forgotten.

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Part I
Introductory Overview

Chapter 1
Historical Overview of Pediatric Headache

Jennifer R. Evan and Christopher B. Oakley

Introduction

Headache is one of the most common conditions to afflict individuals of any and all ages, including children and adolescents. Not only is headache a common symptom of numerous disorders, as well as a frequently cited side effect of many medications, but there exist primary headache disorders that can cause recurring or lifelong headaches without an identifiable secondary disease process or underlying cause. Children are not exempt from these and may present with a primary headache syndrome in childhood or may experience headache from any number of secondary causes that must be considered and identified. Children often first present to their pediatrician for any new symptom or complaint, and a concern of headache may arise during a dedicated visit for a chief complaint of the same or may arise de novo on a routine annual checkup through a review of systems or even by a spontaneously mentioned concern by a child or comment from a parent. Given the range of causes and impacts of headache, from primary to secondary, benign to sinister, or episodic to chronic, the clinician must have a sound knowledge of pediatric headache syndromes and an understanding of the following: how to take a headache history, how to make the correct and accurate diagnosis, when to refer, how and when to evaluate, and how to treat a child with headache, all of which will be discussed in depth in the chapters to follow.

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The special challenge in diagnosing and treating headache in the pediatric populations manifests through the innate vulnerability and sensitivities of children that encompasses taking a history from a child, limiting unnecessary diagnostic studies and scans, education about the condition or disease process to the patient in the context of age and level of understanding as well as with his/her parents or guardians, and weighing risks and benefits of treatment in exposing children to pharmacologic agents and other treatments. The description of the headache obtained through the history is unique in that children may have limited ability to communicate or characterize their experience of head pain, a facet of pediatric headache assessment that lends to the complexity of providing care to children with a complaint of headache. As the child grows cognitively, their experience of headache may change or their descriptors may broaden, which creates inherent variety in the technique and assessment used for children of various ages.

You are a busy pediatrician finishing the well-child visit for 8-year-old Chloe, a healthy and active girl entering the third grade. She was a new patient to your practice less than two years ago when her family moved from out-of-state. As you are finalizing the documentation and printing the after-visit summary, you hear, ''Mommy, my head hurts." Her mother responds with a comforting, "You're probably just hungry, we're going to eat dinner soon." You see that your 4:30 pm patient is checked in. You wonder if this is a new or common complaint of Chloe's or if you should inquire about more details of how often she reports having headache. How do you approach the symptom you just overheard your patient complain of?

Epidemiology

While headache may be initially thought of as a less common complaint in children than in adult populations, recent data from a review of long-term studies has emerged that shows a much higher prevalence than previously known (Fig. 1.1). In one large-scale analysis of 50 population-based studies reporting on clinically diagnosed pediatric headache and migraine from across the world, the lifetime prevalence of headache occurrence in childhood was found to be 58% [1]. The prevalence of a migraine diagnosis in the same review of studies was found to be nearly 8% of all children [1]. In this review, female children were 50% more likely to have headache than male children, and were also more likely to have a migraine than males, though previous epidemiologic studies suggested that the incidence of headache among prepubertal children is similar between males and females, then with a rise in headache occurrence seen in females compared to males after puberty, owing to an influence of menstrual and hormonal inputs to migraine [1, 2]. As children become adults, the lifetime incidence of migraine is important to understand, remaining around 18% of all people, with a peak incidence occurring in

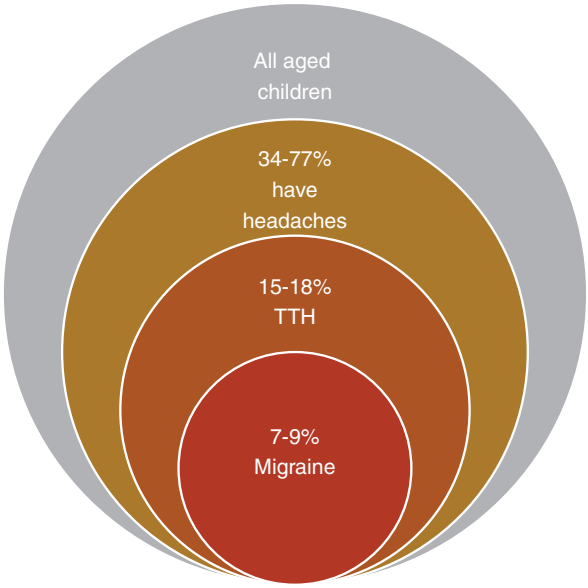

Fig. 1.1 A visual conceptualization of headache prevalence and subtypes, compiled from a review of 50 population-based studies globally plus two geographic specific studies (Turkey, Norway) with a combined 9000 children aged 11–18 years. All diagnoses were based on the International Headache Society (IHS) classification of headache types [1–4]

adolescence [5]. Additionally, the incidence of other migraine subtypes, equivalents, or precursors, such as abdominal migraine, which is frequently encountered in children, is not fully known, and in one study, it was found to be the diagnosis given to 4% of children presenting to pediatric gastroenterology referral [1].

Prevalence of headache does seem to vary among regions, though it is not clear what factors may be responsible for the variations observed, such as internal factors including genetic predisposition and external factors such as cultural perspectives and environmental impact and exposures. In a select population of children within one city in Turkey, the prevalence of primary all-cause headache in children aged 11–18 years was found to be 34% [2]. This number is significantly lower than the non-region-specific review of population-based studies discussed above of 58% of children experiencing headache during their life. In Norway, a study of over 8000 youth aged 13–18 revealed that nearly 77% had experienced headaches in the past year, and 30% of the children reported recurring headaches [3]. The overall calculated prevalence of migraine was also found to be 7%, with a 1.5:1 female-to-male ratio, while the prevalence of tension-type headache was 18% [3].

Age of the child is an additional factor that plays a role in the prevalence of headache and may correlate linearly with the frequency of headache with respect to advancing age groups (Fig. 1.2). Review of both longitudinal and population-based epidemiologic studies including populations from the United States and individual European countries has shown that the rate of headache reported in older age groups, with an average age of 15, is 50–100% greater than the frequency of headache reported in younger age groups, with an average age of 7 years [2]. A similar increase in migraine rates is also seen with older age groups, with one German study finding almost twice the incidence of migraine in 12 to 15-year-old adolescents

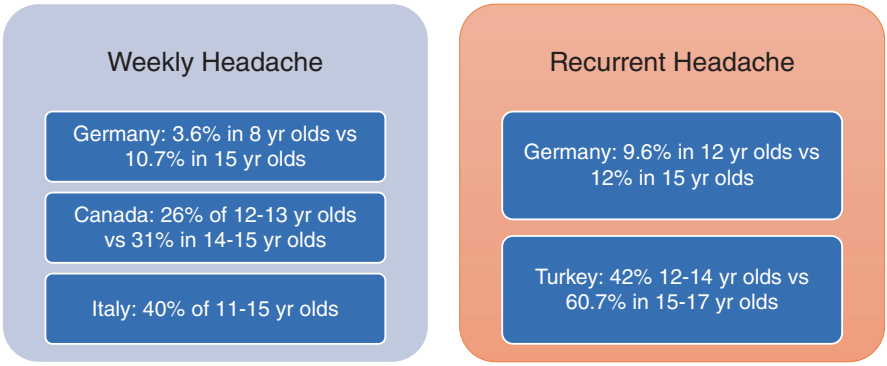

Fig. 1.2 Prevalence of headaches by frequency type with age grouping and country of population study [2, 6]

compared to the 5 to 12-year-old children [2]. The same increase in prevalence with age has been verified in epidemiological studies through the Western and Eastern worlds, including the United States, other northern European countries such as Sweden, and Korea [7]. Though it seems clear that headache experience in children increases with age, the cause of such an increase is likely not attributed to a single factor alone and may be due to a variety of influences including the natural course of the primary headache condition itself as well as headache triggers increasing with age such as psychosocial stressors of school demands, family relationships and function, and emotional stressors.

Headache prevalence in children may be underreported due to a variety of reasons, from minimization or underestimation of frequency by parents to children not vocalizing headache pain out of fear of missing activities or other repercussions, or may not be brought to clinical attention if parents or children are self-treating with over-the-counter medications at home. A study in Brazil found that 6.7% of children were taking nonprescription pain medication for headache treatment at least 5 days each month [2]. Though less commonly seen, the incidence of medication-overuse behavior in children including those who were taking analgesic medication more than 15 days per month was found to be 0.5% in the Head-HUNT-Youth study from Norway [8].

To add another level of complexity to understanding pediatric headache, one must use caution in diagnosing a headache type using the description provided by the child, as common descriptors of pain quality associated with certain headache types may not be a reliable feature in children. One study by Wager et al. of adolescents with headache comparing a patient-completed survey on their headache with the diagnosis by physician using headache classification criteria showed that using children's descriptors of pain intensity and quality had low overall diagnostic utility when matching with diagnosis of tension-type headache or migraine [9]. This is corroborated by other literature showing that the stability of a child's headache diagnosis type is quite low. One study reported that upon re-evaluation 3 years later, up to 50% of children received a different diagnosis [2]. However, the dynamic

nature of headache over time as well as the increase in descriptors and relative experience with age may also cloud the interpretation of this, as children that are assessed for headaches over a course of time may have adapted subjectively to their headache experience or be prone to recall bias. This is contrasted to older children, aged 12–15, who demonstrate more stability of headache diagnosis into adulthood and seem to have a more reliable use of similar descriptors of migraine and tension-type headache as adults [2].

Additionally, numerous studies globally have tracked headache prevalence and reporting rates in children with time, comparing frequency of all pediatric primary headaches in studies from 1950 through the 1980s to equivalent time-span ranges in the 1990s and 2000s, and have found an increasing prevalence of tension-type headache and migraine, including with and without aura types, with rates ranging from 1.5- to 6-fold [2]. True prevalence of headache in children may be difficult to accurately enumerate given the factors of age, culture, socioeconomical factors, access to healthcare, and treatment behavior by parents and children as there is adequate concern that headaches that are experienced but successfully treated with over-the-counter medication are often not reported to providers. An astute provider must consider such factors as the age of the child and independence in self-treating as well as cultural and familial views of headache complaints in order to best assess the diagnosis and guide appropriate treatment of headache in children.

The commonality of headache as a somatic complaint and changing landscape of medicine with a focus on open and thorough provider-patient relationships may explain some increase in the reporting of headaches with time; however, the same increase in prevalence of headache in adults has not been seen in a review of similar literature and has remained relatively stable. This trend suggests that providers and patients are improving in their reporting of headache in youth or perhaps that headache has always been a relatively prevalent experience for children and may have been under-acknowledged and poorly understood in years past.

Historical Background

Headache may very well be one of the oldest conditions to affect humankind. From as far back as the ancient civilizations, through the Medieval times and Renaissance period, to our modern understanding of the symptom, headache has been studied and documented by many well-known figures of history. Interestingly, both prominent figures of medicine and many ensconced in the literary field have described the phenomenon of migraine and sought to characterize the patterns and process from which so many suffered. As our knowledge has grown with time and scientific findings regarding headache pathophysiology, much of what is known now regarding manifestation and treatment may have been explored and experienced thousands of years ago. Understanding how headache and migraine were described by our ancestors and their approach to treatment can broaden our appreciation for the condition and lend a perspective of historical context to the longevity and range of migraine.

Antiquity

One of the earliest mentions of headache sufferers comes from 1500 BCE in the Ebers Papyrus, which accounts a case report of an individual with "a sickness of half the head," possibly referring to the common unilateral headache of migraine [10]. Interestingly, even the Egyptian gods apparently were not immune to headaches as texts have mentioned both Horus and Thoth describing head pain [10].

During the next 1000 years, many continued to experience the condition and likely reported or recorded these recurring headaches upon which later study by those in the ancient Greek and Roman civilizations produced direct characterizations and clinical accounts (Fig. 1.3). Hippocrates, known as the Father of Medicine and to which the field of medicine indoctrinates its oath to practice, is accredited as the first to formally describe in his clinical texts the full experience of what would later be known as classic migraine. In his writing *Aphorisms*, he describes a patient who "seemed to see something shining before him like a light, usually in part of the right eye; at the end of a moment, a violent pain pervened in the right temple, then in all the head and neck … vomiting, when it became possible, was able to divert the pain and render it more moderate" [10, 11]. Hippocrates further wrote of migraine as well as other headache types and advises in his work *Prognosis* that the presence of fever with headache and visual abnormalities should preclude one from diagnosing migraine and should be concerning of other pathologies [10]. Aretaeus of Cappadocia, a Greek physician who practiced in a Roman Province and who was known to have fervently studied the works of Hippocrates, is attributed as the first to name and characterize the most common variations of headache [10]. Cephalalgia referred to the most mild type, cephalea described a longer and more severe headache, and lastly he named heterocrania for a type of headache with often unilateral head pain as well as nausea and vomiting and a concurrent sensitivity to light and odors lasting between a quarter of a day and a full day, the latter of which is very reminiscent of the criteria in our modern age for migraine [10]. Himself a sufferer of this severe type of headache, Aretaeus gives a vivid description of his experience in his manuscript, "the pain … remains in the half of the head. This is called

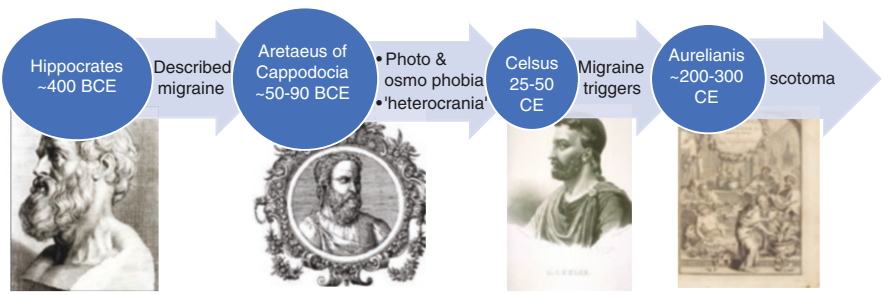

Fig. 1.3 Timeline of Greco-Roman influencers in the documentation of migraine in antiquity [10–15]

heterocrania, an illness by no means mild, even though it appears to be slight … it sets in acutely, it occasions unseemly and dreadful symptoms … nausea; vomiting of bilious matter … there is much torpor, heaviness of the head, anxiety and weariness. For they flee the light; the darkness soothes their disease; nor can they bear readily to look upon or hear anything disagreeable; their sense of smell is vitiated" [10, 11]. His extensive work in clinically describing dozens of conditions, from epilepsy to uterine tumors, exists in an eight-volume treatise entitled *On the Causes, Symptoms and Cure of Acute and Chronic Diseases* [13].

The concept of triggers in provoking migraine seems to be a long-held belief, from environmental factors such as stress to consumed food and drink items. In 50 CE, Celsus was the first to attribute observed triggers to instigating migraine; though not a physician, he writes, "A long weakness of the head, but neither severe nor dangerous, through the whole life. Sometimes the pain is more violent, but short, yet not fatal; which is contracted either by drinking wine, or crudity, or cold, or heat of a fire, or the sun… Sometimes they afflict the whole head, at other times a part of it" [10, 11]. Triggers were further mentioned in 700 CE by Paulus Aegineta, a Greek physician of the Alexandria School of Medicine, who wrote, "… Noises, cries, a brilliant light, drinking of wine and strong smelling things which fill the head. Some as if the whole head were struck, and some as if one half, in which case the complaint is called hemicrania" [11]. Thousands of years later and in current thought, numerous compounds are still associated with an infamy for inducing migraine, from types of alcohol including red wine or nitrites to cheese, chocolate, or synthetic flavor compounds. Interestingly, recent research on the pathophysiology of migraine is exploring triggers such as food cravings in the context of being a prodromal symptom mediated by early migraine manifestations and outputs to the hypothalamus and related structures.

Compounding on the work of his Greek colleagues, Soranus of Ephesus wrote extensively on many body systems including nervous system disorders, and among those headache and migraine. Though his original writings were lost, a Latin translation done by Caelius Aurelianus is survived, and likely inspired Aurelianus to further document headache and migraine manifestations [10]. In his work entitled *De Capitis Passione*, Aurelianus describes "the sudden fogging of vision (nebula), the lines (tractus) resembling the veins in marble called sparks (marmarygae) by the Greeks," likely referring to the visual scotoma of migraine, as well as added symptoms of vertigo, tinnitus, deafness, and lacrimation in association with the unilateral pounding or hammering headache quality and vomiting which he termed "crotophon" [10, 12].

Migraine: It Is in the Name

The first use of the term hemicrania is attributed to Galen in describing the common headaches often afflicting half the head; he described, "a painful disorder affecting approximately one half of the head, either the right or left side, and which extends

along the length of the longitudinal suture ... It is caused by the ascent of vapours, either excessive in amount or too hot, or too cold" [10, 11]. The pathophysiology he believed to be the cause, however, was of the school of thought of disease caused by "four humors": phlegm, blood, yellow bile, and black bile (melancholy), to which he attributed hemicrania to yellow bile, probably due to the presence of vomiting accompanying the headache [11]. Hemicrania, originating from the Greek for hemi meaning "half" and crania meaning "head," was translated directly into Latin, and through a series of spelling and pronunciation changes evolved from hemicrania to "emigrania," then subsequently to migranea and migrana [11]. The term finally made its way to English in 1398 only mildly corrupted in spelling to mygraine, which then experienced a series of spelling changes before finally ending with migraine in 1777, which became universally accepted as the permanent term for the condition [10].

The Middle Ages

Physicians of the Middle East also described headache, including Al Rhazes and Avicenna, the latter of whom termed headaches "soda" from the Persian "sardid" and noted that the pain could be located frontal, occipital, or generalized, but when occurring regularly on one side only was hemicrania [11]. Ibn Sina, also known as Avicenna by those in the West, also thought that odors could be a trigger or exacerbating factor of migraine [11, 16]. In medieval Persian medicine, hemicrania, or "Shaqhiqheh," was well described in many people with unilateral headaches accompanied by nausea, anorexia, photophobia and phonophobia, and hiccups while only some had additional symptoms such as pupil changes, tinnitus, and visual changes or hallucinations, a distinction which is now known as the common migraine compared to the less common classic migraine with aura [17]. Abu Bakr Al-Razi, or Rhazes as is his Westernized name, described even less common migraine types such as a young girl with explosive headache and aphasia with complete resolution, perhaps alluding to a basilar type migraine [17]. Interestingly, numerous secondary headaches, such as from encephalitis/meningitis or tumor, were studied and distinguished from primary headaches, with descriptions of exertional headache and postcoital headaches also being given in Persian texts [17]. Hypothesized pathogenesis was still most consistent with ancient ideas of the four humors, or vital fluids, of the body being out of balance, though Avicenna did make mention that the alteration in the humors affects the brain, meninges, vessels, or extracranial extension of meninges. Numerous triggers were documented by these Persian headache practitioners, including strong odors, ingesting certain foods or alcohol, sleep deprivation, dehydration, overexertion, weather changes, depression, menopausal or postpartum states, as well as head trauma causing long-term headache, such as the case of postconcussive headache [17].

In the twelfth century, Maimonides, a physician of Spanish birth but who practiced in Morocco and Egypt, believed bloodletting as a possible treatment for

headache, specifically mentioning from an artery behind the ear [16, 17]. Though the origin of this curious treatment stemmed from the second-century writings of Aretaeus in the Greco-Roman period, this concept was still utilized in the sixteenth century with Forestus, affectionally called "the Dutch Hippocrates," recommending leeches for bloodletting treatment of headache [16]. Other interesting, albeit uncomfortable, treatments trialed for headache treatment in the past included cupping, blistering, trepanation (holes made in the skull), shaving the head to cut down to the bone, and applying various oils, objects, and occasionally deceased animals onto the head [16].

Despite the volume of clearly described headache and migraine experiences mentioned in the works of the figures of the Greco-Roman civilizations, the spread of this knowledge to other regions was slow during much of the Middle Ages, and through the writings of many figures, it is clear that migrainous visual aura was often interpreted as a divine communication or experience. At the turn of the second century, the musician, poet, and mystic Hildegard of Bingen described her own experience, "I saw a great star, most splendid and beautiful, and with it an exceeding multitude of falling sparks with which the star followed … suddenly they were all annihilated, being turned into black coals …" [11, 15]. Though she interpreted her own experience as a mystical vision, her description bears a strong similarity to the positive phenomenon that occurs in migraine visual aura.

Migraine was also well described by John Hall, a physician, herbalist, and the son-in-law of William Shakespeare, in his medical notebook dated 1644: "Observation XXIII. Good-Wife Bessie aged 40, who once a month (yea sometimes twice or thrice) was grievously pained on the right side of her head, which often ended with vomiting, and in her fit could neither walk nor stand: was cured thus: First, she took this vomit … the vomiting infusion … this wrought six times. For the next day was provided the following pills: Pil de Succin … Cephal Fernel … Pil N … She took three of them before supper, every day till they were spent …" [12]. This practice, historically documented in the writings of many physicians of the past, of using combinations of various herbs via tinctures in treating their patients will be further explored as it relates to the development of pharmaceuticals for the treatment of migraine used in current practice.

Historical Figures with Migraine

Through analysis of letters and writings of many historical figures of the arts and science, it seems at times that migraine is rather ubiquitous. Charles Darwin wrote to his fiancée days before his wedding, "My last two days in London, when I wanted to most leisure, were rendered very uncomfortable by a bad headache, which continued two days and two nights, so that I doubted whether it ever meant to go away and allow me to be married" [15]. Additionally, Darwin made mention of a hereditary component to his headaches that he postulated he acquired from his father [15]. Sigmund Freud also suffered from migraines, mentioning in a letter just prior to the

turn of the nineteenth century, "… my depression left me, not after one migraine, but after a whole series of such states" [15]. He goes on to say in another letter that his health is excellent, with the exception of a "slight migraine on Sundays" [15]. Though reviews of historical documents and personal letters have revealed prominent figures with headache, it can only be inferred by characteristics gleaned from the descriptors whether these headaches were migraines or caused by other common conditions that may not have been recognized, such as hypertensive headache or headache secondary to substance use.

Other literary, musical, and political figures who appear to have endorsed migraine include Edgar Allen Poe, Guy de Maupassant, Leo Tolstoy, Frederic Chopin, Peter Tchaikovsky, Friedrich Nietzsche, Karl Marx, Virginia Woolf, John Calvin, Madame Pompadour, John Churchill, Mary Todd Lincoln, Alfred Nobel, Queen Mary Tudor, and at least a few past Presidents of the United States [15]. Thomas Jefferson divulged in letters to family that he suffered from periodic headaches lasting several days or up to weeks that rendered him unable to work or write, perhaps suggesting that he suffered from episodes of prolonged migraine, or status migrainosus. Politician and writer John Fordyce wrote of his own migraines in his book *De Hemicrania Dissertatio* [11]. It is also known that the prominent English neurologist Oliver Sacks also experienced migraines himself, in addition to seeking to understand his patients' vivid experiences with migraine, which he chronicled with detail and with a certain reverence in his first book aptly entitled *Migraine*.

Recent Past and Modern Age of Headache

As technology and science continued to develop over hundreds of years, the understanding of headache—its manifestations, symptoms, distinguishing features that separate migraine from other headache types, and treatments—arose, and subsequently allowed for a more objective and thoughtful approach to the headache patient. In the early seventeenth century, Thomas Willis, who is known for his work in cerebrovascular anatomy for which the major supratentorial vascular circle is named after, described multiple types of headaches—universal, short or intermittent, and wandering or with uncertain features, among others—as well as studied patterns and habits of those afflicted with headaches [11, 16]. Willis also described headaches associated with emotional trauma or physical injury and noted contributing symptoms such as polydipsia, polyuria, and hunger with headache, likely the earliest observation of prodromal migraine symptoms [11]. Through his experience, he felt that headaches of any type were so common a complaint for people that it was not only rare, but also enviable for someone to report that they had never felt a headache [11].

In the mid-nineteenth century, Hughlings Jackson favored migraine with aura to be a result of vasospasm of the posterior cerebral artery with ensuing electrical discharge of the thalamus and optic pathways, akin to a similar spectrum as epilepsy, thus creating the classic visual aura many reported, and that the headache was a

post-event phenomenon [11]. Perhaps the most notable scholar and clinician of headache was Edward Liveing, whose work not only fundamentally described the phenotypes of migraine encountered by patients but also explored the prevailing theories on pathogenesis. Published in 1873, *On Megrim, Sick-headache, and Some Allied Disorders* discusses etiologies of migraine including the ancient theory of altered balance of bodily fluids or "humors" referenced by Galen and others, "sympathetic and eccentric theories", vascular theories including vasospasm and vasodilation/hyperemia, and the most recent theory of "nerve storms" which Liveing himself ascribed to [11]. This neural spreading mechanism of discharges and vascular reactions of dilation or spasm would remain the prevailing concepts touted by the subsequent headache clinicians, although much discourse would ensue based on regarding which was thought to be the initial event—the abnormal spread of a nerve signal leading to aura and subsequent vascular changes, or vice versa. Both Liveing and Gowers believed that the nerve discharge or "nerve storm" was likely the inciting trigger for the downstream vascular effects, such as vasodilation, that directly cause headache pain [11]. Gowers hypothesized that the hypothalamus and other brainstem nuclei were involved initially based on prodromal and associated features of migraine, and while the headache pain itself was of a more obscure mechanism, it could potentially be manifest through a spread from central nuclei to periphery either through a neuralgia or via meningeal pathways [11]. This early theory of "nerve storms" and spread from central brainstem pathways would be the basis for the later finding of cortical spreading depression and the role it is thought to play in migraine aura propagation.

The concept of cortical spreading depression originated from the work of Aristides de Azevedo Pacheco Leão, a Brazilian scientist who studied epilepsy in rabbits and discovered a decrease in excitability of cortical neurons, or suppression in neural activity, spreading in waves around the initial seizure focus [18]. His work received widespread acclaim and was replicated in further animal studies, which led to the finding that cortical spreading depression (CSD) produced neurogenic inflammation around meningeal blood vessels via the release of pro-inflammatory substances [19]. CSD has also been found to be active in the transmission of nociceptive signals from both central and peripheral trigeminal pathways [19]. The culmination of this work in investigating CSD throughout various brain regions led to the hypothesis that this neural spreading mechanism could be the initial event in migraine and its aura.

Though proving difficult to verify in human patients, the concept of CSD and studies in animals has been largely paramount to the advancing research in migraine pathogenesis. With the advancements in technology and imaging in the twentieth century, researchers in one study were able to objectively quantify the visual aura pathogenesis with regard to CSD in three migraineurs in real time using high-field functional MRI and evaluation of blood oxygen level-dependent signal changes [20]. By mapping the signal changes of blood oxygen to corresponding areas of the visual cortex and matching these with the onset of visual aura and aural features, it was revealed that a focal increase in blood oxygen signal was first seen in an area of extrastriatum and progressed at a rate

of roughly 3.5 mm/min over the occipital cortex followed by a subsequent decrease in signal [20]. Additionally, signal changes reflected the scintillations of the visual aura perceived by the migraineurs across corresponding areas of the visual cortex matching to the retinotopic representation [20]. Numerous studies since 2001 have validated these changes occurring during migraine visual aura using functional MRI and PET, lending further objective evidence of the physiologic changes occurring in the brain before and during migraine aura, and likely mediated by a spreading of neuro-chemical-electric signals [5].

Classification of Headache Types

The classification of headache and diagnostic criteria is defined by the International Classification of Headache Disorders (ICHD), currently in its third updated version since 2018. These criteria have been adopted by the WHO as well as accepted by the ICD-10 for coding and billing purposes of clinical care. The development of the first ICHD in 1988 allowed for the unified defining of headache conditions across practitioners and regions, thereby allowing for more objective tracking of headache epidemiologically as well as for accurately identifying patient groups for research and pharmaceutical development for migraine-specific care.

General classification of headache begins with separation into primary (Fig. 1.4) or secondary categories, with primary headaches being idiosyncratic and independent of any underlying cause, while secondary headaches can be attributed to another medical condition or structural lesion, such as mass or tumor, trauma

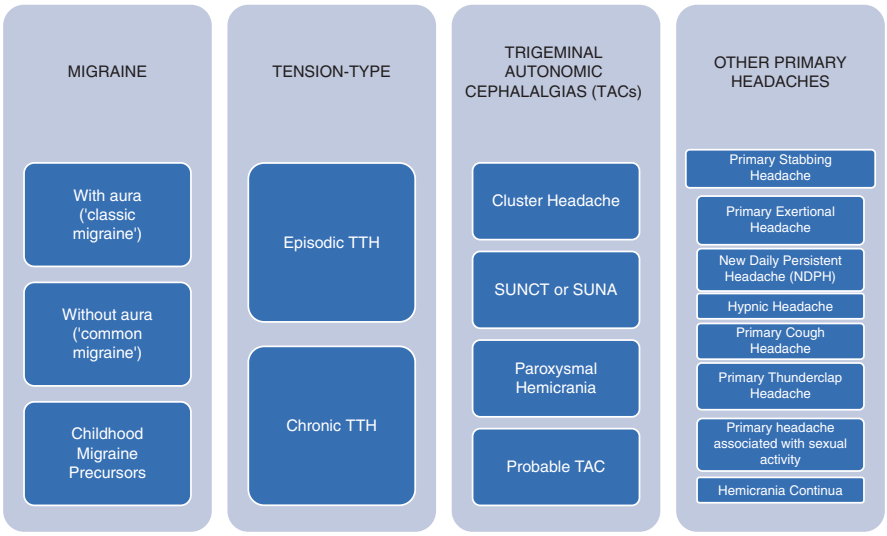

Fig. 1.4 Visual representation of primary headache disorders by type and subtype [21]

including concussion, infection, and metabolic, toxic, or psychological process. Within the primary headache disorder group (Fig. 1.4), the three most common are migraine, tension headache, and trigeminal autonomic cephalalgias, the latter of which cluster headache is the most notorious. Additional primary headache disorders exist (Fig. 1.4), but are much less commonly encountered, including primary stabbing headache, primary cough headache, primary exertional headache, hypnic headache, and new daily persistent headache.

Headache and Migraine Evaluation with Imaging

The utility of working up a pediatric headache patient, including imaging, laboratory evaluation, and ancillary procedures, will be reviewed in detail in a following chapter, but it is worth mentioning that with technological innovation and access to advanced imaging, MRI has been used increasingly in patients with headache. This is often to rule out secondary headache causes, which has led to not only identifying incidental findings nonrelevant to the clinical headache syndrome, but also the discovery of white matter abnormalities seen in many patients with migraine headache. The significance of these small white matter hyperintensities is not clear; however, further research has been done to attempt to clarify whether a relationship exists between the presence or number of these abnormalities and migraine frequency or severity, as well as determine if other structural brain changes occur in patients with migraine such as volume loss or atrophy. This discovery has changed the view of migraine by both patients and clinicians from one of a generally benign condition of painful paroxysms with temporary detriments to quality of life to a condition with concern for potentially harmful long-term changes to the brain and preventing the risk of other events such as ischemic lesions related to migraine pathophysiology. In one large meta-analysis, it was found that a statistically significant association of white matter lesions was present in patients with migraine with aura, as classified by the International Classification of Headache Disorders criteria, but was not found in those with migraine without aura [22]. In a recent small study evaluating structural changes on MRI in pediatric patients with migraine, statistically significant atrophy was found in areas of grey matter in the frontal and temporal lobes, particularly in pathways involved in pain processing [23]. Additionally, there was statistically significant increase in volume in the right putamen in children with migraine when compared to controls, the significance of which is not clear; however, these changes did not seem to correlate to the duration of migraine experience, or frequency or severity of attacks [23]. When considering the findings of this small study in children and in context with the imaging studies done in adult patients with migraine, theories are arising regarding whether some structural changes are a result of years of migraine and whether other changes could be premorbid, possibly reflecting a predisposition for having migraine.

Modern Pharmacologic Treatments of Headache

Pharmacological intervention for pediatric headache will be reviewed in detail in a following chapter, and the background will be discussed here. While it is obvious that physicians of the ancient world used a variety of herbal remedies through tinctures and tonics to attempt to treat headache pain, many of these substances were either not effective or with various ranges of toxicity when consumed or even applied topically. In fact, the origin of the word pharmaceutical, from the Greek word "pharmakon" (Φαρμακον), means drug or poison.

Through time and ensuing observation and clinical research, nociceptive relieving qualities of various compounds have been identified, and some incorporated into medical treatments with controlled and known pharmacologic properties. One of the most well-known medications to have developed from this premise was salicylates, isolated from the willow bark plant that has been used for hundreds of years by ancient peoples. Opiates, though rarely recommended or used in headache/migraine treatment but a common substance for general pain-relieving effect, were identified at their earliest use from the opium poppy flower. While these, and other remedies, were indeed used throughout regions and centuries through a review of anecdotal medical literature, it would still be hundreds of years until a modern substance was discovered for relief of migraine headache.

The first pharmaceutical class discovered for migraine-specific treatment purpose was triptans, agonists of the serotonin 1B and 1D receptors, which came to the market for clinical use in the early 1990s [5]. Triptans mechanistically cause vasoconstriction of cranial vasculature as well as inhibit transmission of signals between neurons involved in the trigeminocervical complex and the trigeminal sensory afferents that propagate the cycle of pain produced [5]. Given the clear role that trigeminal nerve sensory fibers play in transmitting sensation from vasculature and meningeal processes, which is the core of the trigeminal-vascular background of migraine, these medications became among the first to target the underlying mechanism to abort the headache pain of migraine. Over time, some triptans did receive approval for use in pediatric populations, though with more difficulty in studies and less margin of effectiveness over placebo, given that children seem to have a higher propensity to respond positively to non-medication or placebo treatments.

Most recently discovered and utilized in migraine and headache/facial pain treatment are molecules to block the action of calcitonin gene-related peptide, itself a peptide capable of producing vasodilation, and therefore with a prominent role in the trigeminovascular mechanism of headache pain. Monoclonal antibodies developed to antagonize the CGRP receptors or molecules came to clinical availability in 2018, after decades of formulation and development studies [5]. These medications have become one of the most promising new treatments for patients who suffer from migraines, and their use is being explored as well in potentially alleviating other central and peripheral nociceptive conditions such as cluster headache and other facial and head pain conditions.

History of Headache Procedures

With the discovery of X-ray, or roentgenogram as it was first referred to, in the late nineteenth century, the ability to image the head to evaluate for abnormalities particularly with the ventricles was conceived [16]. Prior to this, rudimentary "localization" was limited, and procedures or treatments were aimed at targeting pain atop or proximal to the sight of the offending underlying pathology. Early in the twentieth century, the lumbar puncture was formulated, with Heinrich Quincke being the first to perform the procedure for the evaluation of the spinal fluid, and after whom the spinal needle used in current practice is named [16]. This procedure opened the door to understanding pathophysiology more, as Quincke learned that the majority of the patients on whom he performed lumbar puncture reported relief of headache, and while Edward Flatau verified this same finding, he also reported of possible incidence of headache after lumbar puncture in a young boy, although he attributed it to being most likely in patients who were "weak and pale" [16]. It is now known that removal of cerebrospinal fluid via lumbar puncture during many headaches, including migraine, is often found to be temporarily therapeutic for partial relief of pain, thought to be due to the decrease of pressure against the meninges that are experiencing heightened sensitivity, whether neurochemically or structurally as in some headache causes.

Neurosurgical interventions for head pain also began to take off in the first part of the twentieth century, with Jean Sicard performing periarterial sympathectomy of the temporal artery, Walter Dandy's work on spinal cord ganglia, Herbert Olivecrona's operation on intramedullary tractotomy, and Harvey Cushing's detailed work on the branches of the trigeminal nerve [16]. When compared to the primitive techniques such as trepanation used centuries earlier, the interventional modalities now have come quite a long way from their first conceived forms. Current procedural interventions for headache and migraine patients include a variety of nerve blocks to peripheral nerves, particularly of the branches of the trigeminal nerve but also of the greater occipital nerve, as well as trigger-point injections to target sensitive focal areas related to triggering head or neck pain. Onabotulinum toxin injections over numerous locations on the head and face have also been utilized with FDA approval in the prevention of chronic migraine in adults (patients >18 years old) since 2010. The mechanism of onabotulinum toxin in the prevention of migraine pain is thought to involve aspects of prevention of muscle contraction of face and head muscles affected by heightened pain sensitivity of headache and through the prevention of release of neuropeptides involved in propagating pain, including substance P and calcitonin gene-related peptide (CGRP). Research has shown that these neuropeptides are major components involved in peripheral nerve pain, and it is thought to be based on these peptides activating meningeal vessel dilation, which leads to stimulation of trigeminal sensory nerve endings, thus producing the facial and head pain of headache and migraine [5]. This trigeminovascular theory of pain production is relevant to both migraine with aura, perhaps stimulated by the initial spreading depression stimulus in occipital or brainstem regions and then leading to neurochemical release of these peptides, and migraine without aura.

What is important to note is that while headache procedures such as nerve blocks, trigger-point injections, and onabotulinum toxin injections are a common practice as an intervention to abort and prevent headaches of various types, including migraine, in pediatrics there is limited evidence, approval, guidelines, or protocols available for this patient population. Additionally, these would be offered typically through specialty providers rather than general pediatric practices. Therefore, this is the extent that these procedures will be reviewed.

As you finish up closing the visit, you turn to Chloe's mother and ask, "Is this something Chloe complains of often?" to which she tells you a few times a week, usually after school in the evenings but occasionally on the weekends as well, and that she has given her over-the-counter medication a few times which seemed to work. You nod and acknowledge the information about Chloe and encourage her mother to make an appointment to follow-up for a more thorough review of her headaches, and what things you can do to help lower the frequency and guide management on the cause and treatment if needed. Chloe's mother thanks you for your care and says that she will make an appointment at the front desk for this on checking out.

Headache is an extremely common symptom and condition that is seen throughout pediatrics. Furthermore, it is the most common neurological concern to present to general pediatrics for assessment, evaluation, and treatment. In the following chapters, the various headaches that are often seen in children will be reviewed, as well as how to approach the clinic visit for a headache patient, how and when to evaluate these patients, what comorbidities may be seen with pediatric headache patients, how to approach these patients from a multitiered approach, and what lies ahead for these patients as they transition to adulthood as well as what the future holds for pediatric headache.

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Chapter 2
Pediatric Migraine

Carl E. Stafstrom

Case Vignette

An 11-year-old girl presents with episodes of headache. The location of the headache is bifrontal and bitemporal, and the pain has a throbbing quality ("feels like a hammer pounding my head on both sides plus the top"). About 30 min before a headache, the girl describes visual changes consisting of "colored dots and lines on the left side that move around and later cover both of my eyes. They blur my reading." These spots and lines disappear by the time the headache begins. Headaches are accompanied by nausea but not vomiting. She usually lies down in a dark room and puts a blanket over her head. Sometimes, the headache is so severe it causes her to cry. If a headache gets particularly severe, she will ask her mother for medicine. She is typically given two pediatric ibuprofen tablets (total 200 mg). If she is able to fall asleep, she awakens feeling much better. Headaches have been as short as 30 min and as long as 24 h. Before or during a headache, she does not notice any tingling or numbness in her arms or legs, weakness of any limb, or trouble speaking or understanding others. The frequency of headaches has increased over the past year, from an occasional headache "a couple times a month" to once or twice a week at present. She does not describe a headache trigger; the mother notes that her daughter is moodier the day before a headache and for at least a day after the headache.

At the time of the clinic visit, headache is not present. The general examination is normal, including lack of any tender or sensitive areas on the scalp. There is no tenderness to palpation of the temporomandibular joints, posterior neck, or frontal or maxillary sinuses. Her neck has full range of motion, and there is no meningismus or bruit. Neurologic examination is also entirely normal including sharp, flat optic discs with visible spontaneous venous pulsations.

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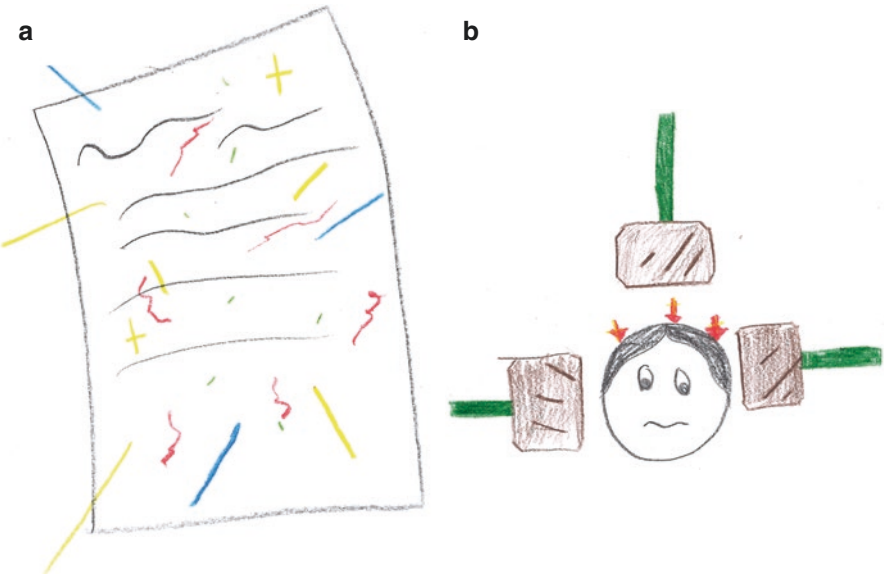

Fig. 2.1 Headache drawing by a 11-year-old girl with migraines. (**a**) About 30 min prior to a headache, her vision is obscured by colored lines and spots (visual scotomata of migraine aura). (**b**) She depicts her headache as three large hammers hitting her head on both sides and the top (indicated by the arrowheads). This pounding pain is characteristic of a migraine diagnosis, verifying the clinical history

When asked to draw a picture showing what it is like to have a headache, the girl draws colored dots and lines obscuring her vision of printed material. About 30 min later, a pounding bilateral headache begins, illustrated by hammers smashing her head from all sides (Fig. 2.1).

Clinical Features of Pediatric Migraine

Headaches are very common in children and are one of the most common reasons for visits to a primary care provider or emergency department. Most pediatric headaches are "primary," that is, migraine or tension type, or are associated with an intercurrent illness such as a viral infection. Clinical evaluation of headaches in children aims to diagnose and classify the headache type, rule out potentially dangerous secondary causes of headache (such as mass, bleed, infection), and formulate an appropriate management plan. The high degree of disability associated with headaches in children, including but not limited to sleep dysfunction, school absence, anxiety, and depression, speaks to the need for early recognition and

optimal management. This chapter focuses on migraine headaches and their mimics for pediatricians and other providers of pediatric primary care. The following chapters will focus on other types of headache in children.

Definition

Migraine is a neurovascular headache disorder. Headache is a core feature of migraine, but migraine involves many other symptoms and dysfunctions, including sensory and autonomic processes [1]. The most recent operational criteria for migraine by the International Committee of Headache Disorders (ICHD) are found in Table 2.1 [2]. This guideline acknowledges that some aspects of migraine in children differ from those in adults. Specifically, to meet the criteria for migraine, childhood migraine can be shorter (2 h compared to 4 h in adults) and can have a unilateral *or* bilateral location (most children actually describe bilateral headache pain). In children, the occurrence of photophobia and phonophobia can be inferred from the child's behavior rather than verbalized (for example, photophobia can be assumed if the child seeks out a dark room). A positive family history of migraine in first-degree relatives provides additional support for migraine as an etiology, but is not a criterion.

In contrast to migraine, tension-type headaches (TTH) often involve band-like, squeezing pain that is more continuous than throbbing, worsens as the day progresses, and lacks key migraine features such as photophobia, phonophobia, nausea, and vomiting. Both migraine and TTH symptoms may occur in the same child. Therefore, it is important to diagnose headache type(s) accurately as the treatment of these primary headache types differs somewhat. For example, the occurrence of both photophobia and phonophobia favors migraine, whereas either symptom in isolation can occur in migraine or TTH.

Table 2.1 Comparison of criteria for migraine in adults and children [2]

Adult	Pediatric
(a) At least 5 attacks fulfilling B–D	
(b) Duration 4–72 h	(b) Duration **2**–72 h
(c) 2 of the following 4: • Unilateral • Pulsatile • Moderate-to-severe intensity • Aggravation/avoidance of routine physical activity	(c) 2 of the following 4: • Unilateral **or bilateral** • Pulsatile • Moderate-to-severe intensity • Aggravation/avoidance of routine physical activity
(d) At least 1 of the following: • Nausea and/or vomiting • Photophobia and phonophobia (P/P)	(d) Same **P/P may be inferred from behavioral observations**
(e) No other explanation	(e) No other explanation

Shaded/bolded text indicates pediatric-specific criteria

Epidemiology

Epidemiological studies of migraine prevalence vary widely depending on the definition of migraine employed, the population studied, and the age ranges included, but it is clear that migraine is very common in children [3]. Before adolescence, about 5% of boys and girls experience migraine. After adolescence, migraine prevalence increases in both sexes, but the occurrence in girls increases more markedly, reaching an eventual female-to-male ratio of about 3:1. Worldwide, in one-third of adults with migraines, the onset is during childhood [4]. These numbers emphasize the magnitude of headache in children, but to understand the actual burden of the disorder, its associated disabilities and socioeconomic costs need also to be considered. Early diagnosis and appropriate treatment may alleviate some of the long-term consequences.

Migraine Stages

A migraine attack typically proceeds through several stages: trigger, premonitory (prodromal) symptoms, aura, the headache itself, and postdromal symptoms. While there is some overlap in the symptoms experienced in these stages, it is important to try to characterize the distinct phases for a given patient (Table 2.2).

Migraine Triggers

The most commonly reported migraine triggers in a child with migraine are stress, lack of sleep, hot environment, bright lights, and noise. Dietary triggers are not usually reported in children and adolescents but are reported in about 1 in 4 adult migraine patients. The time between a trigger and migraine headache is under 3 h

Table 2.2 Migraine stages

	Prodrome	Aura	Headache	Postdrome
Symptoms	Somnolence Hyperphagia Thirst Yawning Cognitive/mood changes Stiff neck	Visual Somatosensory Cognitive/ language	Throbbing Uni/bilateral Nausea/vomiting Photophobia, Phonophobia	Fatigue Somnolence Concentration difficulty Mood changes Muscle pain
Brain area(s) involved	Hypothalamus Limbic system	Cortex	Brainstem Cortex	Cortex Hypothalamus
Physiology	Hypothalamic network dysfunction	Spreading depression	Trigeminovascular system activation	Hypothalamic network dysfunction

for most children. The contribution of geography and climate to migraine triggers may have management implications as well.

The generally accepted consensus is that altered neurovascular homeostasis, with an endogenous or exogenous cause, leads to dysfunction of hypothalamic networks that subsequently triggers a cascade of nociceptive and non-nociceptive symptoms in a genetically hypersensitive/over-responsive brain [5]. In addition to its homeostatic control functions, the hypothalamus is also implicated in pain processing [1], making this a central structure for triggers as well as for each subsequent stage of migraine.

Prodromal Symptoms

Prodromal (premonitory) symptoms are defined by the ICHD-3 as "a symptomatic phase, lasting up to 48 hours, occurring before the onset of pain in migraine without aura or before the aura in migraine with aura" [2]. Prodromal symptoms are usually not painful and may continue into the headache phase and even after the headache has resolved [6]. Up to two-thirds of children and adults with migraine have prodromal symptoms such as yawning, fatigue, neck stiffness, mood changes, gastrointestinal disturbances, difficulty concentrating, photophobia, and nausea. Other symptoms that are seen commonly in children are facial pallor, periorbital dark circles, and osmophobia.

Aura

About 25% of childhood migraines are preceded by aura, defined by the ICHD-3 as a "complex of neurological symptoms that last 5–60 min and are accompanied or followed within 60 min by headache" [2]. Aura is a transient alteration of neurologic function that can affect vision, somatosensory function, or speech (dysphasia). Children may describe more than one type of aura accompanying a migraine attack. Migraine aura has a gradual onset and spreads slowly, correlating with symptom evolution. The latency between the onset of aura and start of headache is typically less than an hour. The end of an aura usually signals the start of headache, but aura can also occur simultaneously with headache. Not all auras are followed by headache.

The physiological basis of aura is thought to be cortical spreading depression (CSD), whereby a wave of depolarization spreads slowly over the cerebral cortex at a rate of about 1–5 mm/min, followed by a wave of hyperpolarization. Aura symptoms arise and abate as the depolarization/hyperpolarization wave passes across an area of cortex associated with the specific neurologic dysfunction (e.g., vision, motor, language) [7]. Importantly, these aura symptoms do not follow a vascular distribution. It is currently uncertain whether and how CSD directly activates trigeminal afferent fibers and initiates the pain cascade that accounts for migraine symptoms (see Sect. 2.1.7).

Most of the detailed descriptions of migraine aura are from adults, in whom the aura consists of visual, sensory, or speech/language symptoms and motor, brainstem, or retinal symptoms. Classically described symptoms of visual aura vary between positive symptoms (scotomata, scintillations, dots, zigzags), negative symptoms (field defects, blurring), disorders of visual perception (macropsia, micropsia), or some combination of these [8, 9]. Visual auras may start in the periphery or center of one or both visual fields [10]. Sensory symptoms can manifest as altered sensation (e.g., paresthesia) or loss of sensation (e.g., hypesthesia) and occur unilaterally or bilaterally, involving face or body. Language impairment can present as naming or grammar errors.

Visual aura is the most common form of aura reported by children with migraine, followed by somatosensory and then language-based symptoms [11]. The precise components of an aura might be challenging for younger patients to describe verbally, making it uncertain how early an aura can occur and whether aura features are different in young children. Children's drawings have proven useful in distinguishing migraine headaches from other headache types and in allowing children to explain their auras and other headache symptoms in nonverbal picture form (Fig. 2.1) [12].

Hemiplegic Migraine

The distinctive feature of hemiplegic migraine is motor weakness as part of an aura which can manifest in conjunction with language, sensory, or visual symptoms. A headache typically accompanies a hemiplegic migraine, and arms are affected more than legs. There is a period of relatively prolonged recovery of weakness after the resolution of headache (<72 h in most patients). Hemiplegic migraine can mimic a transient ischemic attack, stroke, or postictal Todd paralysis [13]. The diagnosis of familial hemiplegic migraine (FHM) is based on clinical features and positive family history in first- or second-degree relatives. Several specific genes have been implicated in FHM, and genetic testing is available but does not alter management [2]. In general, while this a concerning migraine with aura variant that often will scare not only the patient but also their parents, not to mention their pediatrician, it is relatively rare. Given this, when there is a concern for hemiplegic migraine, further evaluation and likely referral to pediatric neurology and/or headache specialist are typically in order.

Migraine with Brainstem Aura

Migraine with brainstem aura, previously called basilar migraine, is reported as the most common subtype of migraine in some pediatric cohorts [14]. Diagnosis requires at least two of the following: vertigo, non-sensory ataxia, dysarthria, diplopia, or altered consciousness. Motor or retinal symptoms are not considered part of brainstem aura [2]. Migraine with brainstem aura is a diagnosis of exclusion, especially with the first presentation, and other etiologies with brainstem symptoms

such as stroke, malignancy, and demyelination must be ruled out. Benign vertigo of childhood is probably a precursor of migraine with brainstem aura in older children. Similarly to hemiplegic migraine, migraine with brainstem aura presentation can be frightening to all involved and typically leads to further evaluation and referrals, as noted above.

Migraine Headache

Migraine headaches have specific qualities and localization. The pain is described as pounding, throbbing, or pulsating by both adults and children. Childhood migraine is commonly localized to frontal-temporal areas (often bilateral) but can be diffuse and poorly localized; occipital localization is reported less often than by adults, who often present with cervical/neck pain as a migraine manifestation [15].

Photophobia and phonophobia together are one of the required associated features or symptoms for a migraine diagnosis according to the ICHD criteria. In clinical surveys, up to 80% of children with migraine describe these symptoms [15]. The neural substrate of migraine-associated photophobia involves photic signals via the optic nerve converging on neurons of the trigeminovascular pathway (the so-called retino-thalamo-cortical pathway). These pathways terminate either in somatosensory cortex (accounting for exacerbation of headache pain by light) or in visual cortex (reflecting abnormal sensitivity to light).

Nausea and vomiting are also frequent accompaniments of the headache phase in children, especially younger ones [16]. Vomiting involves interactions of the central and peripheral nervous systems with the gastrointestinal system via afferent vagal activation. The observation that vomiting is more frequent at younger ages also suggests an overlap with the early-childhood migraine-related disorder, cyclic vomiting syndrome [17].

Postdromal Stage

After the headache resolves, up to 90% of children with migraine report lingering symptoms such as fatigue, dizziness, difficulty concentrating, pallor, anorexia, and mood changes. Return to baseline may take 2 days or more, adding to the burden of the disease. Postdromal symptoms are largely comparable to the symptoms of the premonitory phase, and both are thought to reflect hypothalamic dysfunction.

Migraine and Puberty

Migraines predominate in females after puberty. There is a strong association between migraine and hormonal fluctuations around puberty, with menstrual cycles, with the use of hormonal contraceptives, and during pregnancy [18]. It has been

hypothesized that young females are more susceptible to migraine when menarche occurs early due to the effect of hormonal changes on the hypothalamic-pituitary-gonadal axis and brain development [19]. More than half of adolescent girls with migraines have headaches at the onset of menses [20].

Differential Diagnosis and Episodic Syndromes that May Be Associated with Migraine

Most headaches in children are primary, that is, migraine or tension type, but secondary causes such as described above must be ruled out in any child presenting with headache. Furthermore, many systemic diseases such as acute viral illness, associated disorders such as high blood pressure, metabolic derangement, and psychiatric disease must be considered. In particular, depression and anxiety, so prevalent in children and teenagers, can present with headache as the major manifestation. Headaches not conforming to the accepted criteria for migraine and other primary headaches may be secondary to a psychiatric or systemic disease process.

Several paroxysmal disorders of childhood are thought to be precursors to or variants of migraine [21–23], with periodic and stereotypic manifestations that are separated by symptom-free intervals (Table 2.3). Whereas the specific association between infantile colic and childhood migraine has been well documented, evidence for the other syndromes is less definitive. Though these syndromes are "associated with migraine" by the ICHD-3 diagnostic criteria, with phenotypic similarities, caution should be exercised as their neurobiological mechanisms are still unclear. These migraine "equivalents" or mimics, so prevalent in early childhood, support the notion that migraine pathophysiology evolves over development [24]. See Chap. 3 for further details.

Table 2.3 Episodic disorders that mimic migraine

Condition	Age range	Clinical features	Treatment
Infantile colic	Infancy	Excessive irritability, crying	Reassurance, limit environmental stimulation
Benign paroxysmal torticollis	Early infancy	Unilateral head tilt	Rarely needed
Benign paroxysmal vertigo	Early childhood	Vertigo, dizziness, ataxia	Diphenhydramine or migraine prophylaxis
Cyclic vomiting syndrome	School age	Recurrent vomiting	Intravenous fluids, antiemetics
Abdominal migraine	School age	Abdominal pain, often dull with midline localization	Acute or prophylactic migraine treatment
Alice-in-Wonderland syndrome	School age	Visual distortions of size and shape	Reassurance, migraine prophylaxis

Comorbidities

The numerous comorbidities of migraine in children add to the burden of the disorder. These include both medical (e.g., obesity, sleep disorders, asthma, epilepsy) and psychiatric (e.g., anxiety, depression, attention deficit hyperactivity disorder) conditions [4]. Among the greatest risks of childhood migraine is the eventual "chronification" of the disorder. That is, episodic migraines may become increasingly frequent and evolve into chronic migraine (defined as migraines on 15 or more days per month for at least 3 months), with its associated greater disability. Earlier detection and provision of effective counseling and strategies of pain coping may reduce this transition to chronic migraine. Comorbidities will be discussed in more detail later in Sect. 2.4.

Pathophysiology

The pathophysiology of migraine is complex and multifactorial. Migraine is considered to reflect polygenic hypersensitivity of the trigeminovascular system and cortex to sensory stimuli, leading to a series of pathophysiological changes that culminate in severe, throbbing headache and a variety of systemic symptoms [1, 25]. In brief, activation of the trigeminovascular system (by a trigger such as stress, sleep deprivation, environmental factors, etc.) in an individual genetically predisposed to migraine causes release of neuropeptides such as substance P, neurokinin, and calcitonin gene-related peptide (CGRP) onto blood vessels of meninges. This outpouring of neuropeptides causes vasodilation and increased vascular permeability (that is, meningeal neurogenic inflammation). This pain-related information is transmitted from the meninges along the trigeminal nerve to the brainstem (first-order pathway), then to the thalamus (second-order pathway), and eventually to the cerebral cortex (third-order pathway), where pain is perceived (Fig. 2.2). Theoretically, migraine pain can be modulated at any of the sites along this complex neural pathway. For example, serotonin released from brainstem nuclei in part mediates the flow of pain information to neocortex. Triptans are serotonin receptor agonists that acutely modulate pain circuits. Likewise, monoclonal antibodies to CGRP can block pain at several sites—meninges, trigeminal ganglion, brainstem trigeminal nuclei, and thalamus. Monoclonal antibodies to CGRP are now approved for migraine prevention in adults [26]. Though promising, these agents have not been studied sufficiently in children or approved in the pediatric age range, and their use would be in the province of a headache specialist [27]. Understanding the pathophysiology of migraine will lead to new and improved management options.

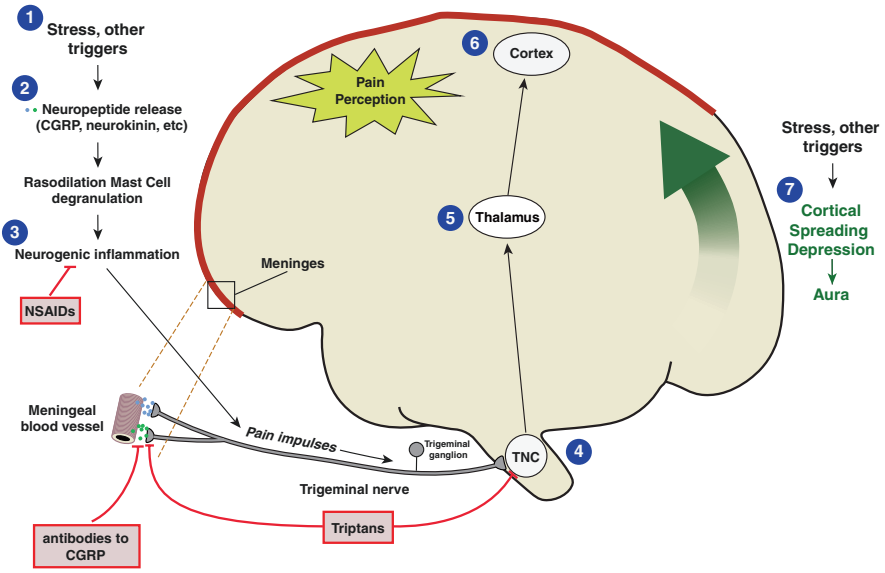

Fig. 2.2 Simplified schematic of migraine pathophysiology. (1) In a child genetically predisposed to migraine, a trigger such as stress, sleep deprivation, or intercurrent illness initiates the migraine cascade. (2) Along meningeal blood vessels, nerve endings of trigeminal nerves release vasoactive neuropeptides (such as calcitonin gene-related peptide (CGRP), neurokinin, substance P, and others). These agents cause blood vessel dilation and mast cell degranulation, leading to neurogenic inflammation (3). The inflamed nerve endings generate pain impulses in trigeminal fibers that travel to the brainstem where they reach the trigeminal nuclei (TN) (4). Impulses then travel to the thalamus (5) and then to cortex (6), where pain perception occurs. Pain can be modulated at numerous sites along this pathway (indicated by red lines): nonsteroidal anti-inflammatory drugs (NSAIDs) reduce inflammation, antibodies to CGRP act at blood vessels as well as at central sites, and triptans activate specific classes of serotonin receptors at multiple locations. Cortical spreading depression (CSD), a wave of neuronal and glial depolarization, can also be initiated by migraine triggers; CSD is thought to underlie the migraine aura that sometimes precedes the headache itself. Data indicate that CSD can also initiate the trigeminal pain cascade (7). Further details can be found in the text and cited references [1, 25]

Clinic Visit, Evaluation

History

The most important part of the clinical evaluation of headache is the history. The headache history will be covered in greater detail in Sect. 2.3 but will be introduced here.

Information should first be sought from the child; the parent can provide clarification if needed. Questions should focus on determining the symptoms of all stages of the headache, from trigger to postdrome. Information should be sought about different types of headaches the child may be experiencing, their onset and trigger

if present, the temporal course of severity and frequency over time, the location and quality of pain, time of day that the headache occurs, and whether the headache wakes the child from sleep. Relieving and exacerbating factors should be asked. It is helpful to know how long the headache lasts with or without intervention such as medication, and what the child does to try to abate the symptoms. Family history is critical as most children with migraine will have another family member with migraines, either currently or previously. Social history should focus on stressors such as family discord, bullying, school performance, and difficulty dealing with siblings, friends, or teachers. Information about lifestyle factors should be obtained, including duration and quality of sleep; appetite, mealtimes, and hydration; amount of caffeine ingested; exercise and activity; and what the child does to relax.

Headache Drawing

Many children, especially younger ones, have difficulty explaining their headache symptoms using words. It is informative to have a child draw a picture of the headache: "What is it like when you have a headache? Please draw yourself having a headache" [12, 28]. Results are often dramatic and informative, both from a diagnostic point of view and from the viewpoint of self-perceived pain and stress (Fig. 2.1). Diagnostically, drawings reliably can distinguish migraine from migraine headaches. Artistic indications of migraine symptoms such as visual changes (obscurations or scotomas of visual aura, photophobia), pulsating pain (objects such as hammers and other pounding objects), nausea/vomiting, or recumbency are highly correlated with migraine as determined by clinical history, whereas band-like or squeezing pain and absence of typical migraine characteristics are more suggestive of non-migraine headaches such as TTH [12]. Children find it empowering and enjoyable to describe their headaches artistically and then explain the meaning of the drawing features, and this method is especially useful in younger children who may lack the verbal sophistication to explain their headaches in medical terms. This technique involves trivial cost, has enormous potential to better understand both the physical and emotional aspects of childhood migraine, and can be readily used in the primary care office.

Physical Examination

The physical examination is a critical part of the headache evaluation [29]. Again, this will be covered in greater detail in Sect. 2.3 but will be introduced here.

In addition to general physical and neurologic examinations, specific attention should be paid to head and neck structures that could help to determine headache etiology and localization (Table 2.4). Included in this "headache examination" are palpation of all structures of the face, head, and neck, looking for areas of pain or sensitivity. For example, palpation of the temporomandibular joint with mouth opening aids in determining

Table 2.4 The headache examination

Maneuver	Purpose
Palpation of cranium	Trigger points
Palpation of sinuses	r/o sinusitis
Palpation of TMJ during mouth opening and closing	r/o TMJ instability
Flexion and extension of neck	r/o meningismus
Listen for temporal bruits	r/o vascular malformation
Neck flexion against examiner's hand on forehead	r/o cervical spine instability
Examination of optic fundi	r/o papilledema

Table 2.5 Red flags during headache evaluation

Headaches becoming more severe or frequent
Increased headache with Valsalva maneuver (sneezing, coughing, bending over, straining)
Explosive headache onset
Secondary risk factors: immune compromise, genetic or neurocutaneous disorder
Headache with altered mental status
Focal neurologic deficits
Early morning vomiting
Waking at night with headache
Papilledema

whether the TMJ is a source of head pain. Palpation of the frontal and maxillary sinuses can uncover underlying sinusitis. Full neck movements should be assured to rule out meningismus. Percussion of the cranium and neck can detect cervical spine-related pain. Having the child exert pressure against the examiner's hand placed on the forehead can indicate cervical spine anomalies if pain is elicited in the posterior neck with this maneuver. Bruits at the temples might indicate an underlying vascular malformation. Complete neurologic examination is essential for elucidation of abnormalities involving mental status, vision, eye movements, speech and language, sensation, strength, reflexes, gait, and coordination. Of foremost importance, funduscopy is critical to rule out papilledema, optic atrophy, and other ocular abnormalities.

When to Worry

As listed in Table 2.5 and elaborated later in Sect. 2.3, certain historical and examination findings should elicit specific concern for an acute neurologic process or underlying pathology. Any focal deficit on neurologic examination, evidence of rapid increase in headache severity, sudden onset of severe headache, and headaches consistently awakening the child from sleep or occurring with vomiting early in the morning should elicit concern and probable urgent neuroimaging with brain MRI scanning.

Most children with headaches fitting the criteria for migraine and with no red flags concerning for secondary headaches do not require evaluation (laboratory testing, imaging, or ancillary testing). There is inadequate evidence to recommend routine blood work such as complete blood count or comprehensive metabolic panel, lumbar puncture (unless meningoencephalitis is strongly suspected), or EEG [30]. If a red flag is present, neuroimaging might be considered, especially in a child less than 6 years of age. Head computed tomography (CT) is often obtained in the emergency room setting if acute hemorrhage or increased intracranial pressure is suspected. Magnetic resonance imaging is preferred, being more sensitive for ischemia, vascular disorders, and neoplasms (especially posterior fossa abnormalities). An EEG would be helpful only if seizure is in the differential diagnosis.

Management

General principles of migraine management in children include reduction of headache frequency, severity, and duration; reduction of overused or poorly tolerated or ineffective medications; improvement in quality of life; and reduction of headache-related comorbidities and psychosocial dysfunction [4, 31–33]. Reassurance and education of the patient and family about migraine are the first step in management. Depending on the degree of disability and disruption of daily activities, a multitiered approach is recommended, using a combination of behavioral (biofeedback, cognitive behavioral therapy (CBT)) and pharmacologic treatments. Management should first address lifestyle modifications and then proceed to medications if indicated (Table 2.6). Intermittent (abortive) medications should be used first, progressing to preventative medications and sometimes to advanced therapies that would be available and offered through specialists in neurology, headache medicine, or pain management (e.g., devices and technology, nerve blocks, trigger point injections, and onabotulinum toxin). Treatment for pediatric headache from a multitiered approach will be reviewed in greater detail later in Sect. 2.5.

Table 2.6 Multitiered approach to migraine management

1. Lifestyle modifications	"SMART" approach: sleep, meals/hydration, activity, relaxation, triggers
2. Acute management	Analgesics Antiemetics Migraine-specific abortives
3. Chronic management	Preventatives Guided imagery/relaxation and other complementary therapies
4. Advanced therapies	Stimulation devices Trigger-point injections (botulinum toxin, etc.)

Table 2.7 "SMART" living for headache control

Sleep	• Based on age: at least 10 h per day in 3 to 5-year-olds, at least 9 h per day in 6 to 12-year-olds, and at least 8 h per day in teenagers • Goal is sufficient sleep, not too much and not too little
Meals (includes discussion of weight management, sufficient hydration, and caffeine avoidance)	• 3 meals per day is optimal—many migraine sufferers report skipping a meal as a trigger • "Enough" fluids are when child needs to urinate every 1–1/2 to 2 h • Caffeine use <2–3 times per week
Activity	• Aerobic exercise several times per week • Too much exercise can be as headache inducing as too little exercise
Relaxation	• Rest and relaxation are important parts of a healthy lifestyle
Trigger avoidance	• Most common migraine triggers in children: stress, intercurrent illness, bright light, noise • Very unlikely that specific foods trigger migraine in children; low utility of eliminating foods from diet—time consuming and not likely to be effective

Lifestyle

Many lifestyle factors influence the susceptibility to migraine. The "SMART" mnemonic (Table 2.7), first published by Dr. Heidi Blume [34], is an easy way for patients and practitioners to remember the critical lifestyle issues that are modifiable in children with migraine. S stands for sleep (amount, quality, daytime somnolence), for which age-related guidelines have been recommended [35]. M stands for meals and hydration, weight management, and avoidance of excessive caffeine usage. A stands for activity, that is, exercise (preferably aerobic); importantly, both too little and too much exercise can exacerbate headaches. R stands for rest and relaxation, key components of a healthy lifestyle that promotes headache control. This is also a good segue to discuss guided imagery/relaxation therapy; these self-meditation techniques can be used by motivated children and adolescents to empower them to achieve some degree of control over their head pain. Finally, T stands for triggers, that is, an attempt to identify headache precipitants and avoid them if possible. Each office visit should include a discussion of these lifestyle modifications and strategies to ameliorate headaches.

Acute Migraine Management

The goal of acute migraine treatment is to relieve the pain and reestablish normal function in 1–2 h. An acute headache should be initially treated conservatively such as having the child relax in a quiet, calm environment and encouraging

a nap if conditions permit. In childhood migraine, "good sleep is like a medicine." Frequent sips of water can enhance hydration status assuming that significant nausea is not present. By the time a child with migraine presents for acute medical management, it is likely that some of these approaches have already been tried. The parent has probably already administered over-the-counter analgesics such as the nonsteroidal anti-inflammatory drugs (NSAIDs) acetaminophen, ibuprofen, or naproxen. At times, the more potent NSAID, ketorolac, may be used to abort migraine. For maximal effectiveness, these medications need to be given early in the headache and at optimal doses. In my experience, parents tend to underdose NSAIDs although the frequency of their administration is often excessive. Generally, it is recommended that analgesics be used no more than three times per week to avoid the development of medication overuse headaches. If nausea or vomiting is prominent, an antiemetic may be helpful. In some cases, the antiemetic can alleviate the migraine pain as well as the nausea (e.g., prochlorperazine). Headache "cocktails" involve multiple medicine classes (fluids, analgesic, antiemetic, possibly triptan). Our clinic provides each child a personalized home therapy plan that includes explicit instructions as to what to take and when to abort a developing or worsening migraine. A typical plan specifies a cocktail including an analgesic, antiemetic, and hydration guideline, and sometimes instructions about a supplemental caffeinated beverage, triptan, or antihistamine.

Triptans are anti-migraine medications that can be considered if NSAIDs are not effective. The class of medication is agonists of serotonin receptor subtypes 1B and 1D, which prevent the release of vasoactive neuropeptides and block pain transmission in trigeminal pathways. Triptans are available in a number of formulations including pills, nasal sprays, and self-injectors. The optimal formulation will be chosen based on a discussion with the child and family. The triptans approved by the US Food and Drug Administration (FDA) are rizatriptan for children 6 years of age and older and almotriptan for children 12 years and above. Other triptans are commonly used to treat pediatric migraine but are not FDA approved (e.g., sumatriptan). A recent practice guideline concludes that the treatments most likely to result in pain freedom at 2 h (compared with placebo) are combination oral sumatriptan/naproxen or zolmitriptan nasal spray [36]. Recommended doses of abortive medications are provided in Table 2.8. Each of these medications is optimally given early in the headache course, with one additional dose allowed 3–4 h later if needed.

If a migraine lasts for more than 72 h, it is called status migrainosus. This prolonged headache needs to be terminated to avoid long-term intractability and unresponsiveness to acute therapies. Treatment of status migrainosus, performed at an emergency department, involves a combination of intravenous fluids, anti-dopaminergic medications, and NSAIDs and sometimes requires hospital admission for more intense treatment, e.g., with intravenous dihydroergotamine [32, 33].

Table 2.8 Selected medications for abortive treatment of pediatric migraine

Drug[a] (classification)	Dose, route	Potential side effects	Comments
Analgesics			
Acetaminophen (Tylenol)	325–650 mg or 160 mg/5 mL every 6 h	Overuse	Often less effective than NSAIDs but useful when NSAIDs contraindicated
Ibuprofen (NSAID) (Advil, Motrin)	10 mg/kg (100–600 mg per age) every 6–8 h	Overuse	Available as suspension, chewable tabs, pills
Naproxen (NSAID) (Aleve, Naprosyn)	220–440 mg or 125 mg/5 mL 5–10 mg/kg every 12 h	Overuse	Effective in adult migraine
Ketorolac (NSAID) (Toradol)	0.5 mg/kg, maximum 30 mg p.o. or IV	Overuse Drowsiness	Can be trialed as 3-day oral taper: day 1: 10 mg t.i.d., day 2: 10 mg b.i.d., day 3: 10 mg once
Antiemetics (dopamine antagonists)			
Prochlorperazine (Compazine)	0.15 mg/kg IV Oral (5–10 mg) or suppository (25 mg) 0.25–0.5 mg/kg/dose every 6–8 h	Sedation May cause extrapyramidal reaction (reduces risk with concurrent diphenhydramine) Prolonged QT interval (get EKG first)	Best efficacy First use should be medically supervised Concurrent diphenhydramine may reduce extrapyramidal side effects
Metoclopramide (Reglan)	5–10 mg tablet or 5 mg/5 mL every 6 h 0.15 mg/kg IV	Sedation May cause extrapyramidal reaction (reduces risk with concurrent diphenhydramine) Prolonged QT interval (get EKG first)	May be less effective than prochlorperazine
Ondansetron (Zofran)	Oral disintegrating tablet 4 mg, solution (4 mg/5 mL) 4 mg every 6 h	Dizziness, palpitations, sedation	Less chance of extrapyramidal side effects
Triptans (serotonin agonists)			
Rizatriptan (Maxalt)	Oral or dissolvable tabs 2.5–10 mg	Flushing Chest pain Drowsiness, dizziness Nausea	Contraindicated in vascular or cerebrovascular disease, pregnancy, hemiplegic or brainstem migraine FDA approved for children ≥6 years old
Almotriptan (Axert)	6.25–12.5 mg tabs	Flushing Chest pain Drowsiness, dizziness Nausea	FDA approved for children ≥12 years old

Table 2.8 (continued)

Drug[a] (classification)	Dose, route	Potential side effects	Comments
Sumatriptan (Imitrex)	Oral tables 25–100 mg Intranasal 5–20 mg Self-injector 6 mg	Flushing Chest pain Drowsiness, dizziness Nausea	Contraindicated in vascular or cerebrovascular disease, pregnancy, hemiplegic or brainstem migraine
Zolmitriptan (Zomig)	Oral or dissolvable tabs 2.5–5 mg Intranasal 2.5–5 mg	Flushing Chest pain Drowsiness, dizziness Nausea	Contraindicated in vascular or cerebrovascular disease, pregnancy, hemiplegic or brainstem migraine

[a]Trade names are listed in parentheses below generic drug names

Special Considerations for Treating Migraine with Aura

There is no specific medication for aura or migraine with aura, other than those already described [13]. Due to their vasoconstrictive properties and a theoretical increase in stroke risk, triptans have been historically considered to be contraindicated in hemiplegic migraine and brainstem migraine. Triptans need not be withheld in migraine with aura [37]. Calcium channel blockers (e.g., verapamil) are often touted as efficacious in migraine with aura, and valproic acid may also be helpful.

Chronic Migraine Management

In general, preventative agents should be considered if the child is experiencing four or more migraines per month, especially if these are debilitating and have not responded to lifestyle changes and abortives. Therefore, it is useful to have families keep track of headaches (symptoms, triggers, frequency, duration) using a log or diary, either in paper form or as a downloadable app. This quantitative method avoids some of the guesswork in trying to keep track of migraines. A headache diary can be a useful discussion tool when deciding whether abortive management is sufficient or whether chronic or preventive management is indicated. Migraines are considered "chronic" when they occur on 15 or more days a month, and at that point, a different management plan should be enacted. Headache severity and degree of disability also factor into decision-making about abortive versus preventative treatment. The degree of disability can be approximated using the simple and freely downloadable PedMIDAS (Pediatric Migraine Disability Assessment, https://www.cincinnatichildrens.org/service/h/headache-center/pedmidas). This 6-question survey, to be completed by the patient (though the parent may help), is validated and useful for assessing current disability and following response to treatment.

The choice of specific preventative medication will depend on a variety of factors including age of the child, sex, comorbid conditions such as sleep disorder, and other lifestyle considerations including cognitive level and willingness or ability to take such a medication more than once a day. The recent childhood and adolescent migraine prevention (CHAMP) study provides some guidance [38]. This randomized controlled study of 361 children and adolescents with episodic or chronic migraines found no significant difference between amitriptyline, topiramate, and placebo. Each treatment improved migraine headache occurrence in about 60% of participants. Notably, each group (including placebo) received extensive counseling about lifestyle modifications and underwent monthly study visits to discuss headaches. Therefore, it has been concluded that children respond favorably to intensive intervention and counseling, whether or not a preventative medication is also prescribed [39]. Importantly, children were excluded from participation in the CHAMP study if they had medication-overuse headaches or continuous headaches, but those two groups are among the most disabled by migraine and there is no evidence-based data to guide their management [40].

Amitriptyline

This tricyclic antidepressant at low doses is an effective migraine prophylactic, especially when combined with CBT. Potential side effects include appetite increase with weight gain, drowsiness (hence, it is taken once daily shortly before bed), and dry mouth. The once-daily dosing is appealing to many children and teenagers. Since amitriptyline often increases appetite, it should be used cautiously in overweight patients.

Topiramate

This broad-spectrum agent, initially developed as an anti-seizure medicine, has been found to be effective in the prevention of migraine headaches in adults and adolescents. In fact, it is the only preventative medication FDA approved for the prevention of migraine in adolescents. Yet, topiramate (and amitriptyline) were not superior to placebo in the above-described CHAMP trial [38]. Side effects of topiramate may include dizziness, drowsiness, appetite decrease, word-finding difficulty, and sensitivity to sunlight.

Cyproheptadine

Cyproheptadine is an antihistamine with anti-serotonergic properties that is quite effective in observational studies for pediatric migraine prevention, especially in younger children. It may help with sleep initiation. As an appetite stimulant, it is especially attractive for use in underweight children.

Propranolol

This beta-blocker is used less often nowadays, though in the past it was a first-line migraine preventative. Side effects may include rapid pulse, palpitations, and depression. As a bronchoconstrictor, propranolol is generally contraindicated in children with reactive airway disease.

When starting a preventative medication, it is important that the family be counseled that it may take 4–6 weeks or longer for the medication to start having a beneficial effect. Therefore, it is important not to give up too early on prevention medicine trials. The "start low-go slow" approach to dosing is suggested.

Aside from pharmacological interventions, CBT is an important and very successful complementary treatment modality [41]. CBT affords the child some control over his or her own physiological variables such as pulse and skin temperature. CBT is limited by the availability of psychologists or others trained in its use, with the dearth of qualified practitioners in many areas. Children and adolescents can also learn self-relaxation or guided imagery techniques, whereby they can exert some control over their own acute pain and disability by learning to breathe deeply and then sequentially activate and relax muscle groups, starting at the head and proceeding down to the feet. Self-relaxation techniques can be easily accessed on a variety of YouTube videos. Acupuncture, physical therapy, and yoga are other non-pharmacological approaches to chronic headaches that have promising effectiveness in children [4]. Behavioral techniques are appealing due to the obvious lack of pharmacological side effects, but they require patience and self-discipline to learn and perform.

Use of complementary medicines is widespread, and many families have already tried some of these before seeking medical attention, thinking that these "natural medications" are safer than conventional pharmaceuticals [42]. Most of these supplements or nutraceuticals have anecdotal evidence only (Table 2.9). Coenzyme Q10 (an antioxidant) and magnesium oxide (which reduces overall cortical excitability) do have some evidence favoring effectiveness in children.

Table 2.9 Selected medications for pediatric migraine prevention

Drug (classification)	Dose	Potential side effects	Comments
Cyproheptadine (antihistamine; some anti-serotonergic properties)	0.25–1.5 mg/kg/day Adult: 4–20 mg/day divided t.i.d.	Drowsiness Appetite increase, weight gain	Especially useful for younger children and those with sleep problems or obesity
Amitriptyline (tricyclic antidepressant)	10–75 mg q.h.s. (1 mg/kg/day)	Drowsiness Appetite increase, weight gain Dry mouth	Benefit is easy use: once-daily dosing at bedtime Best avoided in overweight patients
Topiramate (broad-spectrum anti-seizure drug)	1–2 mg/kg/day once or twice daily Adult: 50 mg b.i.d.	Drowsiness, word-finding difficulty Weight loss Paresthesia Sun sensitivity Renal stones Teratogenicity	Can be used once daily Good choice for overweight patients
Valproic acid (broad-spectrum anti-seizure drug)	15–40 mg/kg/day divided b.i.d. Adult: 500–1000 mg/day	Weight gain Hepatotoxicity Mood/cognitive changes Bruising Pancytopenia Hair loss Rash Teratogenicity	Useful with concurrent epilepsy Requires periodic blood monitoring
Propranolol (beta-adrenergic blocker, antihypertensive)	2–4 mg/kg/day once or twice daily Adult: up to 240 mg/day	Hypotension Palpitations Depression	Avoid in children with reactive airway disease
Magnesium oxide	9 mg/kg/day divided t.i.d.	Diarrhea Rash, itching Nausea Dizziness	Uncertain effectiveness
Riboflavin (vitamin B2)	50–400 mg daily	Yellow urine Diarrhea	Well tolerated Uncertain effectiveness
Melatonin	3–6 mg 1–2 h before bed	Rare nausea, dizziness	May enhance sleep
Coenzyme Q10	50–100 mg daily	Rash Nausea	Uncertain effectiveness

Finally, nerve blocks, trigger-point injections, onabotulinum toxin, stimulation devices, and other new technologies are becoming increasingly available, especially at headache centers.

Back to the Vignette

The child described in the case vignette meets the criteria for childhood migraine. Discussion of management revolved around the multiple-tiered approach, starting with lifestyle factors. For a child of 9 years of age, 9–10 h of sleep per night is considered optimal. Hydration status was addressed, including permission to carry a water bottle at school. She was advised to drink enough water to urinate every 1–2 h during the day. She was urged to eat three regular meals per day and to not skip breakfast. The girl was encouraged to engage in more exercise such as riding her bicycle, walking stairs rather than taking the elevator, and participating in swim lessons. Finally, she was advised to pay attention to possible headache triggers and avoid them if possible. Abortive management included an antiemetic and over-the-counter analgesic, to be used not more than three times per week.

At the follow-up visit 3 months later, headache frequency was unchanged, despite faithful attention to the above lifestyle issues. At that point, it was decided to offer a trial of triptan for acute headache, to be taken as early in the migraine as possible. She was also given a trial of prophylactic medication; amitriptyline was prescribed at a dose of 10 mg to be taken 30 min before bedtime. Prior to initiating amitriptyline, a baseline electrocardiogram was obtained. It was emphasized that this amitriptyline trial was not meant to be a permanent solution, but rather, to get the child out of the frequent headache cycle. We agreed on a 3-month trial, with possible dose increase to 15 or 20 mg before deciding whether this treatment was effective or not.

Pearls

- Migraine diagnosis in children is more common than first thought and typically hinges on the presence of one of the following associated symptoms: (1) photophobia and phonophobia, or (2) nausea or vomiting.
- Aura occurs in about 1/4 of children with migraine. Aura is a transient, fully reversible symptom complex that can include visual, somatosensory, or speech/language deficits. Aura typically occurs within 30 min of headache onset and usually disappears when the headache begins.
- Management of childhood migraine follows a multitiered approach, beginning with lifestyle modifications and then progressing to abortive and/or preventative pharmacological treatments as necessary. CBT and behavioral approaches are also essential.

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Chapter 3
Migraine Precursors in the Pediatric Population

Rashmi Rao

Case
A 2-year-old previously healthy female presents with a maternal family history of migraine without aura. She comes in with episodes of loss of balance. Mom reports that she seemed to lose her balance suddenly. She appears pale and hangs on to her mom's leg during the episode. She is very upset during the episode. Mom has also noticed that her eyes appear to "wiggle" during the episode. The episode only lasts for a few minutes and has occurred at least 10–15 times in the past few months. She goes back to playing after the episode. Her neurological exam is normal.

Abdominal Migraine

Abdominal migraine has been seen in 2–4% of school-aged children [1–3]. Typically, abdominal migraine begins around the age of 7 and then evolves into both abdominal and head pain at the age of 8 to 9 and then into migraine headaches by the age of 10 [4].

Table 3.1 discusses the diagnostic criteria for abdominal migraine per the ICHD-3 criteria [5].

Treatment for abdominal migraine has been suggested for both acute attacks and prevention and, similarly to pediatric headache in general, would follow a multi-tiered approach.

Lifestyle modifications should be reviewed with these children and their parents as this is the foundation for treatment across the board for all pediatric headache patients. Behavioral interventions for prevention that are used for management of

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Table 3.1 Diagnostic criteria for abdominal migraine per the ICHD-3 criteria (1.6.1.2) [5]

A.	At least five attacks of abdominal pain, fulfilling criteria B–D
B.	Pain has at least two of the following three characteristics: 1. Midline location, periumbilical or poorly localized 2. Dull or "just sore" quality 2. Moderate or severe intensity
C.	At least two of the following four associated symptoms or signs: 1. Anorexia 2. Nausea 3. Vomiting 4. Pallor
D.	Attacks last for 2–72 h when untreated or unsuccessfully treated
E.	Complete freedom from symptoms between attacks
F.	Not attributed to another disorder, such as GI or renal disease

migraine headaches including fluids, exercise, sleep, and diet should be discussed with children with abdominal migraine. Complementary and alternative therapies such as, but not limited to, cognitive behavioral therapy, nutraceuticals, acupuncture, and physical therapy could also be considered. The limiting factor here, however, is that patients with migraine precursors tend to be on the younger side, and as such, these may not be ideal as they require understanding and participation that are often hard to achieve in the younger populations. These treatments will be reviewed in greater detail in Sect. 3.5.

Finally, pharmacologic management may be warranted from both a preventative and rescue standpoint. Acute treatment for abdominal migraine is often similar to the treatment that is given for an acute migraine attack. It may often include a triptan, analgesic, as well as antiemetic. Due to the presence of nausea, vomiting, or anorexia, a nonoral formulation of one of these classes of medication may be most beneficial [6]. There has been evidence that nasal or subcutaneous sumatriptan has been effective in acute treatment of pain [7] and has been seen with sumatriptan nasal spray [8]. For prevention of these episodes, a migraine preventative such as cyproheptadine or propranolol could be considered as well [9, 10]. There have been reports of other medications such as pizotifen [11] and flunarizine [12] to be successful in prevention. Other migraine preventatives such as amitriptyline and topiramate have not been studied specifically for abdominal migraine but are often used as they are typical migraine prophylactic medication used in pediatrics.

Cyclical Vomiting Syndrome

Cyclical vomiting syndrome can be seen most commonly in childhood but is increasingly being recognized in adulthood as well. The ICHD-3 criteria as per Table 3.2 describe these attacks of intense nausea and vomiting that are stereotypical [5]. Nausea and vomiting can occur at least 4 times per hour and last for at least 1 h and up to 10 days [5].

Table 3.2 Diagnostic criteria for cyclical vomiting syndrome per the ICHD-3 criteria (1.6.1.1) [5]

A.	At least five attacks of intense nausea and vomiting, fulfilling criteria B and C
B.	Stereotypical in the individual patient and recurring with predictable periodicity
C.	All of the following: 1. Nausea and vomiting occur at least 4 times per hour 2. Attacks last for ≥1 h, up to 10 days 3. Attacks occur ≥1 week apart
D.	Complete freedom from symptoms between attacks
E.	Not attributed to another disorder, such as GI disease

Also described are phases for cyclical vomiting including the interictal or well interval, prodromal phase, emetic phase, and recovery phase [13]. These phases help guide treatment as discussed further below. The prodromal phase lasts for approximately 1.5 hours and can be the period where children can experience nausea, pallor, and/or irritability [13]. The emetic phase is once the vomiting has begun [13]. Finally, the recovery phase is when the child is at the end of vomiting until he or she is able to tolerate a full diet. It typically lasts for 6 h [13].

Differential diagnosis for cyclical vomiting syndrome should include not only GI disease, but also a metabolic disorder or cannabinoid hyperemesis syndrome. A metabolic syndrome should be considered when there are seizures or developmental delay in the history, food triggers (high-fat or high-protein meals, fasting, or illness), or encephalopathy with attacks [14]. Hyperemesis cannabinoid syndrome should be considered in adolescents or adults with new-onset cyclical vomiting [15]. Typically, these patients have attacks and report an increase in hot showers [16].

Due to the significant nausea and vomiting potential for disability in cyclical vomiting, both acute and preventative treatment should be considered in addition to lifestyle modifications where applicable as well as consideration of complementary and alternative therapies mentioned above and again in more detail later in Sect. 3.5. Lifestyle modifications as in migraine headaches should include identification of triggers, diet, fluids, exercise, and sleep. This was shown to decrease the frequency of episodes in 70% of patients without the use of medications [13]. Additionally, vitamins and supplements including coenzyme Q10, riboflavin, and carnitine have also been used as a preventative for cyclical vomiting syndrome [4].

Acute treatment for cyclical vomiting can include rehydration, analgesics, and antiemetics. Again, as with abdominal migraine, nonoral formulations such as nasal sprays, injections, and suppositories can be considered. In addition, subcutaneous and nasal spray sumatriptan [17] or nasal zolmitriptan [4] may provide relief. Lorazepam has also been used as children can experience anxiety with these episodes due to potential prolonged time frame [13], and oftentimes sedation can help relieve an episode.

Children who are refractory to treatment with these abortive agents may benefit from aprepitant [18]. Aprepitant is a neurokinin-1 receptor antagonist. It is typically used in preventing chemotherapy-induced nausea or vomiting. Aprepitant is typically administered for children greater than 20 kg at 125 mg on day one and then at

80 mg on days 2 and 3. For children >15 kg and <20 kg, aprepitant is 80 mg for 3 days. For those less than 15 kg, it is administered at 80 mg on day 1 and 40 mg on days 2 and 3 [18].

A key concept to keep in mind when working with a patient or family who has been diagnosed with cyclical vomiting syndrome is that these patients can quickly become dehydrated, which will only exacerbate the situation. This is why it is imperative to recognize cyclical vomiting syndrome as the diagnosis and to treat each event aggressively from the beginning. If home abortive regimens fail, then hospitalization may be necessary. Aggressive IV fluid hydration as well as deep sedation can help shorten attacks. Medications include IV lorazepam or IV diphenhydramine [13]. In addition, IV chlorpromazine with diphenhydramine has also been shown to be beneficial [13].

Preventative treatment options for cyclical vomiting include cyproheptadine and topiramate; however, amitriptyline has been identified as the most effective agent [13]. Typically, its dose is started at 0.2–0.3 mg/kg/day and increased by 10 mg/week to avoid side effects. Doses greater than 1.5 mg/kg/day require monitoring for QT prolongation. Frequently, higher doses of amitriptyline are found to be beneficial, and therefore monitoring of drug levels can be beneficial [13]. Aprepitant has also been studied and can be beneficial as a preventative as well [18].

In addition, children with cyclical vomiting syndrome can experience comorbidities including anxiety, fatigue, and postural orthostatic tachycardia syndrome (POTS) [13]. Particularly, anxiety has been found in 47% of children with CVS [19]; therefore, adequate treatment of underlying anxiety can also prevent future attacks. Comorbidities seen in pediatric headache patients will be reviewed in greater detail later in Sect. 3.4.

Benign Paroxysmal Vertigo

Benign paroxysmal vertigo typically occurs between the ages of 2 and 5 [20]. It is the most common cause of dizziness in the preschool-age group [21]. Children are typically unable to describe the feeling of vertigo to parents, and therefore parents often describe the pallor, eye movements, and fearfulness. Although it could be mistaken for a seizure, there is no alteration of consciousness during these events. Table 3.3 describes the ICHD-3 criteria required to make a diagnosis [5]. In addition, it is important that neuroimaging is performed to rule out a posterior fossa lesion [5].

Children with benign paroxysmal vertigo typically outgrow it after 2 years, but some may continue to have episodes that persist into adolescence [4]. In addition, children with BPV typically have a family history of migraine, and 20–33% develop migraines in the future with some having an increased likelihood of migraine with vertigo.

Because most episodes of BPV are typically short in duration, an acute treatment is not generally indicated. However, if attacks are relatively frequent, then a

Table 3.3 Diagnostic criteria for benign paroxysmal vertigo per the ICHD-3 criteria (1.6.2) [5]

A.	At least five attacks fulfilling criteria B and C
B.	Vertigo that occurs without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
C.	At least one of the following five associated symptoms or signs: 1. Nystagmus 2. Ataxia 3. Vomiting 4. Pallor 5. Fearfulness
D.	Normal neurological examination and audiometric and vestibular functions between attacks
E.	Not attributed to another disorder, particularly posterior fossa tumors, seizures, and vestibular disorders have been excluded

preventative may be considered. Again, lifestyle modifications, as noted above, as well as complementary and alternative therapies could be considered. However, given that most of the children with this are toddlers and the disease process is relatively self-limiting, most providers choose not to start a preventive medication unless events are frequent. If a preventive medication is needed then those that are used for migraine prevention such as cyproheptadine can be considered [4].

Benign Paroxysmal Torticollis of Infancy

Benign paroxysmal torticollis of infancy is a rare syndrome that consists of stereotyped episodes of torticollis, which was first described in 1969 by Snyder [22–24]. Episodes of benign paroxysmal torticollis of infancy are often described as stereotypic events that recur with a periodicity. Table 3.4 describes the diagnostic criteria per the ICHD-3 criteria [5].

Typically, these events begin between the ages of 8 months and 2 years of age. It typically improves by the age of 2 and resolves by the age of three to four [4]. It has been noted that girls have a higher prevalence of benign paroxysmal torticollis of infancy [25]. In addition, genetic mutations that have been associated with familial hemiplegic migraine including CACNA1A and PRRT2 have been associated with children with BPT that may have also had a family history of episodic ataxia, hemiplegic migraine, or paroxysmal tonic upgaze [4]. Children with benign paroxysmal torticollis of infancy have a higher likelihood of developing abdominal migraine as well as specifically migraine with vertigo.[4]

Diagnostic studies such as MRI brain and cervical spine are often recommended to rule out a posterior fossa or craniocervical lesion, and EEG could be considered if there is any concern for possible seizure from the parent's or guardian's description of the events.

Treatment for benign paroxysmal torticollis of infancy is typically not recommended, as episodes are brief and infrequent. However, with prolonged episodes,

Table 3.4 Diagnostic criteria for benign paroxysmal torticollis per the ICHD-3 criteria (1.6.3) [5]

A.	Recurrent attacks (typically monthly) in a young child, fulfilling criteria B and C
B.	Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
C.	At least one of the following five associated symptoms or signs: 1. Pallor 2. Irritability 3. Malaise 4. Vomiting 5. Ataxia (seen more in older children than in the affected age group)
D.	Normal neurological examination between attacks
E.	Not attributed to another disorder—the differential diagnosis includes gastroesophageal reflux, idiopathic torsional dystonia, and complex partial seizures. Specifically, the posterior fossa and craniocervical junction should be considered, as a congenital or acquired lesion may produce torticollis

there has been concern that motor delay can occur. It is unclear why motor delay occurs, but it may be due to the frequency of episodes not allowing the infant to make motor milestones or secondary to an underlying genetic cause [4]. There have been no studies on therapeutic interventions for patients with BPT due to the limited number of cases. Case reports have suggested the use of a migraine preventative such as topiramate between 2 and 4 mg/kg/day for those cases that are more frequent [25]. In addition, cyproheptadine has been discussed, but since this occurs in infancy, the safety of cyproheptadine in this age group has not been addressed [25].

Infantile Colic

Infantile colic was initially described by Wessel in 1954 [26]. It is described as paroxysms of irritability or crying in a healthy, well-fed infant [26, 27]. Incidence of colic is variable and has been reported in 5–26% of infants [27, 28]. The crying can begin during the second week of life and will peak at 6 weeks [27]. Colic typically resolves between 12 and 16 weeks of age [27].

The cause of colic has been relatively unknown but is thought to be multifactorial. Theories for colic include gastroesophageal reflux, gas, milk-protein intolerance, food allergies, gut dysmotility, maternal anxiety and depression, and paternal depression [27, 28]. However, despite these theories of the cause of colic, there have been no treatment trials that have helped to understand the etiology of colic [27, 28].

More recently, colic has been described in the migraine literature by parents of children with migraine headaches, and those parents have identified a history of colic when they were babies [4]. In addition, it has also been seen that a maternal history of migraine is a precursor for the development of colic in infants [27, 28]. Maternal depression was also found to be associated with infantile colic, and maternal anxiety was only noted to have a borderline association with colic [28]. However, it is unclear if the maternal depression is a by-product of the colic or a preexisting

Table 3.5 Diagnostic criteria for infantile colic per the ICHD-3 criteria (A1.6.4) [5]

A.	Recurrent episodes of irritability, fussing, or crying from birth to 4 months of age, fulfilling criterion B
B.	Both of the following: 1. Episodes last for ≥3 h/day 2. Episodes occur on ≥3 days/week for ≥3 weeks
C.	Not attributed to another disorder, particularly failure to thrive

comorbidity [29]. The International Classification of Headache Disorders (ICHD) third edition lists colic in the appendix as an episodic syndrome that may be associated with migraine [5]. The diagnostic criteria for infantile colic per the ICHD-3 criteria are listed in Table 3.5 [5].

Prenatal guidance should be considered with mothers who have migraine and especially those with migraine and mood disorders. Counseling of the possibility of colic may decrease the potential for parental concern in the future [28].

There is no recommended treatment for colic at this time. Other potential causes of colic should be investigated to determine if a medical intervention is needed. Otherwise, treatment should primarily be supportive for the parent as there is a higher potential for shaken baby syndrome in infants with colic [4]. Therefore, parental interventions such as decreased stimulation, rocking, swaddling, and white noise could be considered [27].

Case Follow-Up and Discussion

Following her initial presentation, a further workup with sedated MRI of the brain is obtained. The imaging is normal. Her pediatrician provides reassurance at the time after neuroimaging is negative. She is diagnosed with benign paroxysmal vertigo of childhood, and while a trial of medication was discussed, given the infrequent nature of the events and the short duration, mom decides to observe for now as she has reassurance that it is nothing serious or ominous.

She returns to her pediatrician at the age of 6 due to episodes of nausea and vomiting. Her mother notes that these occur on a monthly basis, and they can predict the day that it will start. She has no headache associated with the events. She has a full GI workup which is normal. This time she is diagnosed with cyclical vomiting syndrome, another migraine precursor. Options including cyproheptadine and amitriptyline are reviewed as potential preventative options. Given the general benign nature of cyproheptadine, mom chooses cyproheptadine to start in attempts to prevent the events. The episodes space out over the following year, and it is ultimately decided to discontinue her cyproheptadine at her 8-year well-child visit after 6–12 months without symptoms.

Finally, she returns to her pediatrician at the age of 14 for headaches that have been ongoing for the past 1 year, starting about 6 months after menarche. The headaches are described as unilateral but sometimes bilateral, throbbing, and associated

with nausea, light and sound sensitivity, as well as vertigo. Her headaches last for 3 hours and occur once a week. Her pediatrician diagnoses her with migraines, which is not surprising given her history of migraine precursors. Treatment with a multitiered approach is reviewed including starting a daily prophylactic with amitriptyline as well as offering rizatriptan for as-needed abortive treatment for a migraine attack.

This case demonstrates how migraine precursors can present and evolve throughout childhood. It is important for migraine precursors to be considered in the differential when seen in general pediatric practice. In doing so, the direction for evaluation and treatment may turn completely different and ultimately lead to more reassurance along with a better understanding of what is going on and what to expect. Additionally, by correctly identifying a migraine precursor, treatment considerations may be more targeted and ultimately more successful in helping the child feel better.

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Chapter 4
Other Primary Headaches Commonly Seen in Pediatrics (Tension Type, Cluster, TACs)

Jessica Klein

Case #1
A 13-year-old girl presents to her pediatrician for her yearly well-child check. Upon review of systems, she indicates that she has been having headaches for the last year at an average frequency of once per week. Upon further questioning, she describes the pain as a pressure-like sensation most prominent in the temple areas bilaterally, with extension in a band-like pattern around the entire head, a 3 out of 10 on a pain scale, typically lasting for 30–60 min. She denies associated nausea, vomiting, photophobia, or phonophobia. She has not missed any school or activities due to the headaches. The headaches typically occur on school days, and she notes that they greatly improved over the summer. On examination, she has normal vital signs including a normal-for-age blood pressure and normal body mass index. Her general health examination is normal, as are her neurologic and funduscopic examinations.

Case #2
A 17-year-old young man presents to his primary care physician for evaluation of headaches. He reports that he is having episodes of intermittent severe headaches lasting for 1 week at a time. He describes that during the week, he will have between 1 and 5 discrete headaches per day, each lasting for about 20 min with resolution in between. The head pain is described as 10 out of 10 on a pain scale, located around his right eye, with associated redness and tearing of that eye. He feels agitated during the episodes and is unable to participate in normal daily activities during the headache. He brings pictures of his face during an attack, and the pictures reveal right-eye injection with tearing, and the physician also notices ptosis of the right eyelid evident in the photographs. His last headache episode was 2 weeks ago. He

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recalls having had 7 such attacks occurring approximately every 4 months. On examination, he has normal vital signs including a normal blood pressure and body mass index. His general examination is normal, as are his neurologic and funduscopic examinations. Of note, there is no cranial nerve deficit seen on examination.

Case #3
A 16-year-old young man presents to his pediatrician for evaluation of headaches. He reports having two attacks per year of severe debilitating headaches. When these attacks occur, he will have severe left orbital pain lasting for 5 min, which recurs a total of 10 times per day with resolution in between episodes. He feels agitated when this occurs and describes the pain as a 10 out of 10 on a pain scale. He has associated swelling of the left forehead, and when he has looked in the mirror during an attack, his left pupil was smaller than the right. The episode will go on like this for an average of 2 weeks and then typically does not recur again until 6 months later. On examination, he has normal vital signs including a normal blood pressure and body mass index. His general examination is normal, as are his neurologic and funduscopic examinations.

Tension-Type Headache

Tension-type headache is likely to be underreported and many times is brought up during routine checkups. With a prevalence over a lifetime of between 30 and 78% and with impacts on quality of life, tension-type headache is an important diagnosis to recognize and treat [1]. Patients with chronic tension-type headache require particular attention, because it is in this group of patients that quality of life suffers. In addition to headaches, these patients have a higher risk of generalized hyperalgesia and lowered pain threshold, which seems to stem from central sensitization of pain pathways over time [2].

As defined by the International Classification of Headache Disorders third edition (ICHD-3), infrequent tension-type headache is diagnosed by meeting the following criteria:

A. At least 10 episodes of headache occurring on <1 day/month on average (<12 days/year) and fulfilling criteria B–D
B. Lasting from 30 min to 7 days
C. At least two of the following four characteristics:
1. Bilateral location
2. Pressing or tightening (non-pulsating) quality
3. Mild or moderate intensity
4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
1. No nausea or vomiting
2. No more than one of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Based on the frequency and chronicity of the headaches, tension-type headache can be categorized into infrequent episodic (as above), frequent episodic, or chronic tension-type headache and further subcategorized into those with pericranial tenderness and those without.

The pathophysiology behind tension-type headache is not fully known but is thought to be due in part to peripheral myofascial tension in the head and neck regions, leading to hyperexcitability of the peripheral nerves [3]. Many patients with tension-type headache have pericranial tenderness on examination. It is postulated that repetitive nociceptive signals from the head and neck muscles lead to central sensitization of the nerves at the level of the trigeminal nucleus and/or the dorsal horn of the spinal cord, ultimately contributing to the altered pain tolerance and hyperalgesia seen in patients with tension-type headache [4]. Central sensitization of nociceptive pathways leading to head pain is supported by research done on neurotransmitters such as nitric oxide (NO), calcitonin gene-related peptide (CGRP), substance P, vasoactive intestinal polypeptide (VIP), and neuropeptide Y.

Spinal pain pathway sensitization as well as activation of periarterial sensory nerves leading to arterial dilatation have been associated with release of NO [3]. The role of NO in head pain pathophysiology is further supported by studies showing that patients with chronic tension-type headache who received a nitric oxide synthase inhibitor had reduced head and neck tenderness and reduced headache while those receiving a nitric oxide donor had headaches triggered [5–7]. The triggering of a delayed headache after NO donor administration that was seen in patients with chronic tension-type headache was much less likely in healthy controls, thereby suggesting that patients with a baseline amount of central sensitization to pain are at higher risk of the pain-inducing effects of NO [7].

Calcitonin gene-related peptide (CGRP) is a neuropeptide that has gained recent attention with the advent of CGRP blocking agents for the treatment of migraine. CGRP levels have been shown to be elevated in patients with migraine [8]. In contrast, patients with tension-type headache have normal CGRP levels as well as normal levels of other neuropeptides (substance P, vasoactive intestinal polypeptide (VIP), and neuropeptide Y) [9, 10].

The treatment of tension-type headache mirrors the treatment used for migraine. Of paramount importance is addressing and modifying suboptimal lifestyle factors. Patients should be counseled on the importance of these factors in treating their headaches and empowered to do so. While lifestyle modifications will be touched on here, they will be reviewed in greater detail in Sect. 4.4.

Sleep disturbance is a common comorbid concern in patients with headache syndromes. The patient should be counseled on the optimal age-appropriate sleep duration, developing and maintaining a bedtime routine and appropriate bed and wake times, avoiding frequent daytime napping, and avoiding afternoon caffeine. The clinician should also inquire about snoring, nighttime awakenings, and how refreshed the patient feels after a full-night sleep in order to screen for sleep apnea.

Optimal hydration, nutrition, and exercise as well as avoiding caffeine overuse are also important in the treatment of headaches. Hydration with mainly water should be optimized, and we suggest utilizing a urination frequency and quality goal in order to assure that good hydration is being met. We routinely counsel patients to drink as much water as is needed to produce at least 6 urinations per day and to aim for clear/light urine color. We like this approach rather than simply setting a goal of how many ounces per day to drink since it will account for differences in physical activity (for example, a hot day spent exercising outside would require more water intake than a cool day spent relaxing indoors). Optimal nutrition should also be emphasized. This includes eating regular meals and avoiding skipping meals, eating a healthy variety of foods, and weight management if needed. Routine cardiovascular exercise is also recommended, and we try to provide an attainable goal of 20–30 min 3 times per week. Caffeine should be avoided in excess and particularly in the afternoon hours as this may interfere with sleep.

Given that pain and mood oftentimes affect each other, stress management and addressing comorbid mood disorders are essential in treating headaches. It may be helpful to employ the use of validated depression and anxiety screening questionnaires in order to uncover these concerns. Once recognized, assuring that the patient gains access to the mental health services they need is important. In the treatment of migraine, certain types of psychological therapies, including cognitive behavioral therapy and biofeedback therapy, have been shown to be useful for pain control, and these may be used if appropriate in other headache types as well.

There are multiple complementary and alternative treatments that may be used to treat primary headache syndromes including tension-type headache, such as but not limited to physical therapy, massage therapy, craniosacral therapy, and acupuncture, where appropriate. The risks and benefits of these types of therapies should be discussed with the patient and caregiver. Further review of complementary and alternative treatments can be seen in Sect. 4.4.

Medications are used to treat tension-type headache when the headache burden is high or when lifestyle modifications have not provided enough benefit. Though most of the literature support for medications and vitamin supplements to treat headache comes from migraine studies, these same medications and vitamin supplements may be used to treat tension-type headache. Which medication or vitamin to choose is often a decision made based on the desired side effect profile. For example, a patient with difficulty falling asleep may benefit from amitriptyline or gabapentin, while a patient with obesity may benefit from topiramate. Pharmacological interventions will be further reviewed in greater detail in Sect. 4.4.

Trigeminal Autonomic Cephalalgias (TACs)

The trigeminal autonomic cephalalgias are a group of primary headache syndromes that are unilateral with associated predominant parasympathetic autonomic symptoms ipsilateral to the head pain. Given the differential diagnosis that should be considered

in this group of patients, it is recommended to obtain brain imaging with MRI brain and, depending on the type of TAC, to also obtain MRA head and neck, MRV head, and/or special sequences through the pituitary and cavernous sinus regions [11]. Treatment of this group of headache syndromes should still focus on lifestyle modifications as reviewed above, but there are some specific treatment recommendations pertaining to TACs, which we will also review below. The reader should keep in mind that since the TACs tend to be adult-onset disorders, most of the literature pertaining to treatment comes from adult studies rather than pediatric studies.

Cluster Headache

Of the TACs, cluster headache is the most common though still overall quite rare (only 0.1% prevalence in adults) with a male predominance of 3–4:1 and typically starting in the 20s or 30s [12].

As defined by the ICHD-3, cluster headache is diagnosed by meeting the following criteria [1]:

A. At least five attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting for 15–180 min (when untreated)
C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
• Conjunctival injection and/or lacrimation
• Nasal congestion and/or rhinorrhea
• Eyelid edema
• Forehead and facial sweating
• Miosis and/or ptosis
2. A sense of restlessness or agitation
D. Occurring with a frequency between one every other day and 8 per day
E. Not better accounted for by another ICHD-3 diagnosis

The differential diagnosis of cluster headache is wide and includes other primary headache syndromes that can mimic cluster headache, but also importantly includes causes of secondary headache, such as tooth impaction, acute-angle glaucoma, sinusitis, temporal arteritis, Tolosa-Hunt syndrome, trigeminal neuralgia, malignancy (pituitary tumors among others), cerebrovascular events such as dissection or infarction, and obstructive sleep apnea. For this reason, an MRI brain with specific pituitary and cavernous sinus sequences is recommended, and an MRA of the head and neck should be considered. In addition, an evaluation for sleep apnea should be considered in appropriate patients [11].

Typically, cluster headache attacks occur for weeks to months at a time followed by a period of remission, though patients with chronic cluster headache may not have times of remission. Cluster headache has a few features that if present in the

patient history can help the clinician distinguish it from other primary headache syndromes. It has typical triggers of alcohol consumption, histamine release, or nitroglycerin consumption and often responds to high-flow oxygen administration [1].

The pathophysiology of cluster headache is thought to involve the autonomic fibers of the trigeminovascular system as well as the hypothalamus. The autonomic fibers account for the associated parasympathetic symptoms and signs and the posterior hypothalamic region account for the cyclical pattern of the attacks, which tend to occur around the same time of the year for an individual patient [13]. While our knowledge surrounding calcitonin gene-related peptide's role in headache syndromes, specifically in cluster headache, is still evolving, CGRP levels have been shown to be elevated during cluster headache attacks and are reduced after administration of a triptan medication. CGRP is a potent vasodilator and leads to neurogenic inflammation as well as pain sensitization.

It is likely that CGRP plays an important role in the pathophysiology of cluster headache, and in fact the FDA recently approved a CGRP blocking monoclonal antibody for prevention of episodic cluster headache in adults [14].

Treatment of cluster headache involves optimizing lifestyle factors as reviewed above as well as in Sect. 4.4 coming up, but there are additional treatments that pertain to cluster headache specifically. For acute treatment of an attack, oxygen administration has been shown to be helpful in 56–82% of patients [15], and the recommendation is to administer 100% oxygen at a rate of between 6 and 12 liters per minute [16], while there is some suggestion that rates as high as 15 liters per minute may be used. Triptans have also been shown to be effective, particularly intranasal zolmitriptan and subcutaneous sumatriptan [16].

From a prophylactic standpoint, while many of the typical migraine preventative agents are used, verapamil in particular has Level C evidence categorizing it as possibly effective as per the American Headache Society (AHS) treatment guidelines for cluster headache [16]. Topiramate and lithium are also used, and melatonin may be helpful as an adjunct therapy [11]. More recently, occipital nerve blocks including a steroid ipsilateral to the head pain have been shown to be effective with Level A evidence from the same AHS guidelines [16]. A course of high-dose oral steroids may also be used as a transitional therapy while getting an oral daily preventive agent on board [11].

Paroxysmal Hemicrania

Similar to cluster headache, the onset of paroxysmal hemicranias is typically also in adulthood. Its prevalence is less than that of cluster headache. It has, however, been reported in children with similar symptoms as are seen in adults [17]. There is no male predominance [1].

As defined by the ICHD-3, paroxysmal hemicrania is diagnosed by meeting the following criteria [1]:

A. At least 20 attacks fulfilling criteria B–E
B. Severe unilateral orbital, supraorbital, and/or temporal pain lasting for 2–30 min
C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
• Conjunctival injection and/or lacrimation
• Nasal congestion and/or rhinorrhea
• Eyelid edema
• Forehead and facial sweating
• Miosis and/or ptosis
2. A sense of restlessness or agitation
D. Occurring with a frequency of >5 per day
E. Prevented absolutely by therapeutic doses of indomethacin
F. Not better accounted for by another ICHD-3 diagnosis

The differential for paroxysmal hemicrania is similar to that of cluster headache; therefore, it is recommended to obtain brain imaging with MRI brain and MRA of the head and neck [11].

What sets paroxysmal hemicrania apart from cluster headache are that the duration of each pain attack is shorter and it responds universally to indomethacin. Treatment should begin with an indomethacin trial, with a final total daily dose between 75 and 225 mg. A typical trial course is 2–4 weeks, and the patient should be placed on a gastritis preventative medication during this course [11].

Hemicrania Continua

Hemicrania continua shares the same associated features and response to indomethacin therapy as paroxysmal hemicrania but is diagnosed when the headache has been present without remission for >3 months. Patients with hemicrania continua may have migrainous features such as photophobia, phonophobia, and/or nausea but that are distinguished from migraine by its ipsilateral autonomic symptoms and response to indomethacin [1].

As defined by the ICHD-3, hemicrania continua is diagnosed by meeting the following criteria [1]:

A. Unilateral headache fulfilling criteria B–D
B. Present for >3 months, with exacerbations of moderate or greater intensity
C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
• Conjunctival injection and/or lacrimation
• Nasal congestion and/or rhinorrhea
• Eyelid edema

• Forehead and facial sweating
• Miosis and/or ptosis
2. A sense of restlessness or agitation, or aggravation of the pain by movement
D. Responds absolutely to therapeutic doses of indomethacin
E. Not better accounted for by another ICHD-3 diagnosis

The differential diagnosis of hemicrania continua is similar to that of cluster headache and also includes brain metastases and cerebral sinovenous thrombosis. As such, it is recommended to obtain an MRI brain with MRA head and neck, and MRV head should be considered [11].

Treatment should start with an indomethacin trial up-titrating as needed to a total maximum daily dose of 225 mg with subsequent dose weaning to the minimum effective dose. Once stable, a trial of weaning off indomethacin completely should be attempted. Other medications such as gabapentin, verapamil, topiramate, and melatonin may also be used [11].

Short-Lasting Unilateral Neuralgiform Headache Attacks

This subgroup of trigeminal autonomic cephalalgias includes short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and these are classified by how short in duration each pain episode is and the type of associated autonomic symptoms.

As defined by the ICHD-3, the overarching category of short-lasting unilateral neuralgiform headache attacks is diagnosed by meeting the following criteria [1]:

A. At least 20 attacks fulfilling criteria B–D
B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal, and/or other trigeminal distribution, lasting for 1–600 s and occurring as single stabs or a series of stabs or in a sawtooth pattern
C. At least one of the following five cranial autonomic symptoms or signs, ipsilateral to the pain:
1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or rhinorrhea
3. Eyelid edema
4. Forehead and facial sweating
5. Forehead and facial flushing
6. Sensation of fullness in the ear
7. Miosis and/or ptosis
D. Occurring with a frequency of at least once a day
E. Not better accounted for by another ICHD-3 diagnosis

SUNCT meets the above criteria and must include both conjunctival injection and lacrimation ipsilateral to the head pain, while SUNA meets the above criteria but with only one or neither of conjunctival injection and lacrimation. There may be some difficulty distinguishing short-lasting unilateral neuralgiform headache attacks from trigeminal neuralgia as autonomic symptoms may be seen with both. When autonomic symptoms are present in trigeminal neuralgia, however, they tend to be milder than those seen with SUNCT or SUNA [1].

The differential diagnosis of SUNCT and SUNA is similar to that of cluster headache, plus the addition of primary stabbing headache, trigeminal neuralgia, and a posterior fossa lesion. As such, it is recommended to obtain an MRI brain with MRA head and neck. Additionally, specific sequences looking at the trigeminal nerve may be considered [11].

The short-lasting unilateral neuralgiform headaches respond best to the prophylactic use of lamotrigine, though topiramate and gabapentin are also used in addition to other agents. Specific to this group of headaches is treatment with IV lidocaine, which may be helpful acutely and in some provides lasting benefit for months [11]. They do not tend to respond to indomethacin, which can be an important distinguishing factor from paroxysmal hemicrania or hemicrania continua.

Return to Clinical Cases

Case #1

A 13-year-old girl presents to her pediatrician for her yearly well-child check. Upon review of systems, she indicates that she has been having headaches for the last year at an average frequency of once per week. Upon further questioning, she describes the pain as a pressure-like sensation most prominent in the temple areas bilaterally, with extension in a band-like pattern around the entire head, a 3 out of 10 on a pain scale, typically lasting for 30–60 min. She denies associated nausea, vomiting, photophobia, or phonophobia. She has not missed any school or activities due to the headaches. The headaches typically occur on school days, and she notes that they greatly improved over the summer. On examination, she has normal vital signs including a normal-for-age blood pressure and normal body mass index. Her general health examination is normal, as are her neurologic and funduscopic examinations.

Headache type: Tension-type headache

Subtype: Based on the frequency of 4 headaches per month, she fits within the subcategory of frequent episodic tension-type headache.

Treatment: Reassurance is provided that she is having tension-type headaches. Lifestyle modifications are reviewed, and physical therapy is offered if needed. No daily prophylactic is suggested but she is told that she can use ibuprofen as needed to treat the acute headaches.

Case #2

A 17-year-old young man presents to his primary care physician for evaluation of headaches. He reports that he is having episodes of intermittent severe headaches lasting for 1 week at a time. He describes that during the week, he will have between 1 and 5 discrete headaches per day, each lasting for about 20 min with resolution in between. The head pain is described as 10 out of 10 (actually described higher but was told that 10 was the top pain that can be reported) on a pain scale, located around his right eye, with associated redness and tearing of that eye. He feels agitated during the episodes and is unable to participate in normal daily activities during the headache. He brings pictures of his face during an attack, and the pictures reveal right-eye injection with tearing, and the physician also notices ptosis of the right eyelid evident in the photographs. His last headache episode was 2 weeks ago. He recalls having had 7 such attacks occurring approximately every 4 months. On examination, he has normal vital signs including a normal blood pressure and body mass index. His general examination is normal, as are his neurologic and funduscopic examinations. Of note, there is no cranial nerve deficit seen on examination.

Headache type: Cluster headache

Subtype: Based on the frequency and periods of remission between attacks, he fits within the subcategory of episodic cluster headache.

Treatment: MRI brain and MRA of the head are obtained out of precaution and are normal prior to initiating treatment. For his treatment, while lifestyle modifications and complementary therapies are reviewed, he is in need of both preventative and rescue medications. Verapamil is initiated for prophylaxis. For rescue, a combination of high-flow oxygen via non-rebreather mask along with a triptan (intranasal zolmitriptan) is prescribed. Additionally, a course of prednisone is offered to help try to ease the cluster headaches for a bit while these treatments are started.

Case #3

A 16-year-old young man presents to his pediatrician for evaluation of headaches. He reports having two attacks per year of severe debilitating headaches. When these attacks occur, he will have severe left orbital pain lasting for 5 min, which recurs a total of 10 times per day with resolution in between episodes. He feels agitated when this occurs and describes the pain as a 10 out of 10 on a pain scale. He has associated swelling of the left forehead, and when he has looked in the mirror during an attack, his left pupil was smaller than the right. The episode will go on like this for an average of 2 weeks and then typically does not recur again until 6 months later. On examination, he has normal vital signs including a normal blood pressure and body mass index. His general examination is normal, as are his neurologic and funduscopic examinations.

Headache type: paroxysmal hemicrania

Subtype: episodic paroxysmal hemicrania

Treatment: MRI brain and MRA of the head and neck are obtained out of precaution and are normal prior to initiating treatment. Given that these occur only twice a year,

a daily preventative is discussed, but ultimately it is decided to focus on rescue for when these episodes occur. Indomethacin is offered to initiate at onset at 75 mg daily with option to titrate if needed. He is able to continue this for about 3 weeks to get him past his episodic paroxysmal hemicrania attack periods.

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Chapter 5
Common Chronic Daily Headaches in Pediatrics

Valentina Popova and Rachel Penn

Case #1
A 16-year-old female with a past medical history of anxiety presents to your clinic for frequent headaches. The patient reports that she started getting headaches in the second grade. At first, they were less bothersome, but over the past few years, her mother notes that she has had to miss many more school days and her grades have suffered. Patient reports that she has about 6 "bad" headaches per month, which last for about 3–4 days at a time. She says that she has been treating her headaches with 400 mg ibuprofen, which makes the pain more bearable, but it always seems to come back the next day. She tells you that she is taking ibuprofen most days of the week. She reports that her headaches are usually associated with significant nausea. They are usually on the left side but can involve her whole head. Her exams, including neurological and fundoscopic exams, are normal.

Case #2
A 12-year-old male with no past medical history is presenting with headaches. Parents report that about 6 months ago, the patient suffered a head injury while playing soccer. Dad states that he saw one of his son's teammates knock heads with him on the field. Patient reports that he does not clearly remember the incident and mostly remembers the beginning and end of the game. He states that he saw some stars in his vision and bent down to the ground. However, he resumed

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play within a few seconds. Dad reports that his playing seemed off the remainder of the game, and the patient does report that he felt a little bit more off balance. That night, the patient started complaining of a headache that was on both sides of his head, but more on the right side where he was hit. It was initially associated with some nausea. He could not fall asleep that night due to the pain, so his parents took him to the ED. There they did a non-contrast head CT, which was normal, and he was advised on concussion precautions. He was told to take some acetaminophen as needed for his headaches. The patient went back to school that week. He reports that initially his head felt better, and so did his nausea, but never fully resolved. His parents state that since then he has been complaining of a headache to some degree of a daily ongoing headache with spikes to a more severe headache at least three times a week. He also started to miss some school days due to headaches. Headache was now fully on both sides of his head with no associated nausea, photophobia, or phonophobia. He does endorse continued sensation of feeling off balance intermittently. His exam is normal including a full neurological exam.

Case #3

A 10-year-old male with no significant past medical history comes in for his well-child check over the summer, where, on review of systems, it is found that the patient also has a history of some teeth grinding, for which he has a mouth guard, as well as frequent headaches. He reports that the headaches feel like a squeezing around his whole head, and he uses his hands to circumvent his head when describing the pain. He denies any nausea or vomiting with the headaches and states with certainty that lights and sounds do not bother him when he has the pain. He also denies any GI symptoms with his headaches at all. Mom notes that he is able to play video games while having some of these headaches. Thinking back, mom mentions that his headaches have probably been occurring 4 or 5 times a week lasting at most up to a few hours at a time for pretty much the entire last school year. His general and neurological exams are completely normal.

Case #4

A 15-year-old female with no significant past medical history presents with a daily headache for 4 months. She reports that she does not remember ever having significant headaches in the past until June 11, 2020. This was the day after she went on a school trip to an amusement park. She developed a headache the next day that progressed throughout the morning, and it has not gone away since then. She reports that pain is only in both temples as well as in the front of her head and feels like a pressure, but when it exacerbates, the pain can be throbbing and pulsating. The pain is there all the time; she does not have any pain-free time. She ranks the baseline pain at 2/10, and when it exacerbates, it can go up to 6/10 for a few hours. She denies any nausea or vomiting. She does say that maybe once a month or so with a really bad day, she will have light and sound sensitivity, but this is not typically there either. Her exam is completely normal, including a full neurological exam.

Chronic Migraine

Pediatric migraine, as discussed in Chap. 2, is one of the most common and disabling headaches in childhood. Not coincidentally, chronic migraine is one of the most common chronic headaches in children. Much of which was discussed in Chap. 2 is pertinent for chronic migraine but will not be focused on here. Instead, what is highlighted here is that which is specific to chronic migraine.

What sets chronic migraine apart from episodic migraine is the frequency of the headaches and migraines as well as potentially the length of time that the headaches and migraines have been occurring. Chronic migraine is defined by the ICHD-3 (for episodic migraine ICHD-3 criteria, see Chap. 2) as headaches on 15 or more days per month, with 8 or more days characterized as migraine (see Chap. 2 for ICHD-3 migraine criteria), for at least 3 consecutive months [1]. While the exact prevalence of chronic migraine is hard to know as so many pediatric chronic headache patients are non-differentiated into a specific subtype, the estimates are around 2% for children and adolescents [2]. Chronic migraine is highly disabling in childhood and adolescents, leading to a much lower quality of life because of the impact on school functioning and participation in family and social ctivities. Studies have found that children from lower socioeconomic classes are more likely to develop chronic migraine [2–4]. Additionally, migraine patients who go undiagnosed, and thus untreated, are more likely to progress to chronic migraine as several studies have found that inadequate treatment of episodic migraines increases the chances for the progression to chronic migraines [2, 5]. This highlights the importance of recognizing the presence of migraines in children and adolescents and treating accordingly, especially if they start to increase in frequency, dysfunction, or disability.

As such, it is important to look at factors that have beenfound to predispose individuals to the development of chronic headaches, including migraines. Most individuals present with episodic migraine syndromes, and there are several factors that are thought to contribute to the development of chronic migraine. One hypothesis, is that those with comorbid mental health concerns, such as anxiety or depression, are at an increased risk of developing chronic migraine, as well as those who have suffered a stressful life event. What is interesting is that while these factors seem to exacerbate headaches and migraines when they are already present, they does not seem to be direct correlation to the actual development of migraines or headaches. Additionally, other somatic conditions such as arterial hypertension, allergic rhinitis and sleep disturbaces are thought to contribute to the progression from episodic to chronic migraines. While medical confounders are thought to possibly contribute to the progression or development of chronic migraine, there are other factors that are thought to contribute as well. For example, caffeine consumption, especially when in excess for an extended time period, as well as alcohol consumption are thought to favor progression to chronic migraine [2, 5, 6].

Medication overuse has also been implicated as a contributing factor to the progression from episodic migraines to a chronic migraine. To this point, medication-overuse headache occurs in up to 35% of adolescents with frequent daily headache

and increases the likelihood of the development of chronic migraine [7]. Taking abortive medications such as opioids (* opioids should not be used in the treatment of headaches in general, especially in children and adolescents), ergotamine, triptans, and combination analgesics on more than 9 days per month or over-the-counter analgesics on more than 14 days per month can lead to medication-overuse headache [1]. When medication overuse is seen, the recommendation is to focus on prophylactic treatments rather than acute interventions, and in fact, the removal of the overused rescue treatment may be beneficial, as it is possibly a contributing factor to the chronic headache or migraine. Of note, depending on the agent that is being overused, it may need to be weaned rather that stopping abruptly to avoid potential withdrawal [7].

Chronic Post-traumatic Headache

Head injuries occur often, probably much more often than anyone recognizes or realizes, in children and adolescents. Fortunately, the majority of cases are classified as mild, and full recovery is seen within a few weeks. Unfortunately, for those who do not recover within a few weeks, the recovery process is less predictable and can take months to years. There is even a very small proportion of head injury patients who have lingering symptoms, including headaches, ongoing without end. It is these groups with the most persistent symptoms that are the most difficult to treat. Of note, adolescents tend to be at a higher risk of prolonged symptoms following mild head injury than younger children. Additionally, high school athletes are more likely to have a prolonged recovery period as compared to college athletes, albeit this may be skewed as the desire to remain at play could affect the validity of the length of the recovery period [8].

Not only is age a factor, so is sex when considering head injury sequelae. Female sex is associated with a higher risk of sustaining concussion and reporting concussion-like symptoms. These gender-related differences are even more pronounced in childbearing years, signifying that hormones may play a role [8]. Additionally, genetics and family history as well as past medical history may contribute to the development of post-traumatic headache. Some studies have found that a family history of migraine was found in 82% of those with headaches at 3 months postinjury. However, other studies revealed that neither prior headache treatment nor a prior history of migraine was associated with a prolonged recovery [9]. Patients who had a prior history of mood disorder or learning disability are at an increased risk of prolonged recovery, as well as those who have a history of prior concussion [10].

The ICHD-3 criteria classify mild head injury as injury that is not associated with loss of consciousness for more than 30 min, GCS score <13, post-traumatic amnesia lasting for more than 24 h, altered level of consciousness for more than 24 h, or imaging evidence of a traumatic head injury such as intracranial hemorrhage and/or brain contusion. The injury is associated with one or more of transient

confusion, disorientation, or impaired consciousness; loss of memory of events immediately before or after the injury; and two or more symptoms suggestive of mild traumatic brain injury including nausea, vomiting, visual disturbances, dizziness, vertigo, or impaired memory or concentration [1].

Headache is often one of the first symptoms to develop and is one of the last symptoms to resolve following a head injury. Chronic post-traumatic headache is defined as a new headache disorder or a preexisting headache that worsens in frequency or severity after head injury and continues to recur for a period of at least 3 months. The onset of headache should be within one week of (a) a minor head injury, (b) regaining consciousness, and (c) discontinuation of medications that may impair sensation of pain [1, 8]. It is estimated that chronic post-traumatic headache may affect up to approximately 8% of children and adolescents. Post-traumatic headache is commonly associated with other physical, cognitive, and emotional symptoms of concussion, which contribute to the overall disability and quality of life. It is commonly seen with dizziness, sleep disturbances, and mood disorders, specifically anxiety and depression [8–10].

The pathophysiology of post-traumatic headache is poorly understood and is likely to involve several mechanisms. Even small minor head injuries can cause widespread stretching or shearing injuries to the axonal networks. These axonal injuries may be associated or followed by metabolic cerebral disturbances, cerebrovascular inflammation, or alteration in the normal cerebral blood flow. The abnormal release of excitatory neurotransmitters and other neuro-inflammatory peptides may mediate the onset of headache. Additionally, there is speculation that head trauma may trigger an underlying primary headache disorder through induction of cerebrovascular inflammation, trigeminovascular dysfunction related to injury, and dysfunction of cervical facet joints from trauma [11].

As mentioned above, those children that develop chronic post-traumatic headache are thought to have a predisposition to a headache diagnosis, and it is thought that the injury may unmask the child's predisposition to a primary headache disorder. It is important to recognize that neither the severity of head injury nor the mechanism of the injury predicts the incidence or prognosis of post-traumatic headache. In fact, headaches are more likely to develop in children who suffer minor head injury as compared to those who sustain a moderate or severe head injury [8].

The clinical features of post-traumatic headache in children and adolescents can be similar to those of migraine, tension-type headache, or even a mixture of the two. In adults, there are reports of less common headache types following head injury including cluster headache, cervicogenic headaches, occipital neuralgia, and hemicrania continua. Regardless of the clinical phenotype, prognosis for children and adolescents with chronic post-traumatic headache is favorable. Unfortunately, this does not necessarily mean a quick resolution. Several studies over the years have shown the persistance of post-traumatic headache at 3 months, 6 months, 12 months, and even longer in a small percentage of patients following head injury. When post-traumatic headaches persist for over a year following a head injury, there is no time table for when these headache may resolve [12]. Of note, the incidence of headache appeared lower in concussed athletes versus the general population at 1 week and

1 month of head injury; however, this may be secondary to underreporting in this population due to the desire to return to play [8, 11, 12].

Chronic Tension-Type Headache

Tension-type headache is the most common primary headache disorder that is diagnosed in children and adolescents and was discussed at length in Chap. 4. As with migraine, as noted above, it is not a coincidence that chronic tension type is a common chronic headache in children. Much of which was discussed in Chap. 4 is pertinent for chronic tension-type headache but will not be focused on here. Instead, what is highlighted here is that which is specific to chronic tension-type headache.

As reviewed in Chap. 4, the ICHD-3 criteria classify tension-type headaches as headaches with two of the four following features: bilateral location, pressing or tightening quality, mild or moderate intensity, or not aggravated by routine physical activity, as well as both of the following features: no moderate-severe nausea or vomiting, and no more than one of the following: photophobia, phonophobia, or mild nausea [1]. There may be associated pericranial muscle tenderness. Episodic tension-type headaches become chronic tension-type headaches when the headaches occur on 15 or more days per month for 3 months or more; additionally, specifically for chronic tension-type headache, the headaches should occur more than 6 months out of a year (or more than 180 days) [1].

In children and adolescents, the prevalence of chronic tension-type headache ranges from 0.1 to 20% depending on the type of population study. Tension-type headaches affect boys and girls equally. It is thought that the etiology of chronic tension-type headache involves a complex interaction between genetic and environmental factors, as stress and psychosocial factors are thought to play a large role in its cause and maintenance. From a biological perspective, both a general hypersensitivity to pain and impaired nociception from pericranial myofascial tissues are thought to play roles in tension-type headache, suggesting that both central and peripheral mechanisms may be important contributing factors [13]. While peripheral mechanisms may play a larger role in episodic tension-type headache, central mechanisms are probably more important in chronic tension-type headache. Supporting this hypothesis is a study comparing MRIs of patients with chronic tension-type headache, medication-overuse headache, and a healthy subpopulation, which found decreased gray matter in areas of the brain involved in nociception in those with chronic tension-type headache [14].

Children with frequent episodic tension-type headaches are at an increased risk of progressing to chronic tension-type headache. Extrapolating from adult data, it is possible that medication overuse, muscular stress, oromandibular dysfunction, psychiatric disorders, and psychological stress are risk factors for progressing to chronic tension-type headache [15]. Children and adolescents with a history of stressful life events as well as chronic disease are at a higher risk for chronic

tension-type headache. There is limited data in adults and children that nighttime bruxism has an association with tension-type headache [16].

While episodic tension-type headaches have not been found to cause significant impairment in functioning, chronic tension-type headaches, as true with essentially all chronic headache subtypes, have been found to significantly impact the life of children and adolescents. This impact can be seen in all aspects of life from school performance to social functioning, which in turn leads to an overall lower quality of life. Not surprisingly, there are associations suspected between chronic tension-type headache and adverse life events, high-perceived stress, emotional internalization, mood dysfunction, anxiety, and sleep disorders [14–16]. While tension-type headaches are often dismissed, they should be taken seriously, especially when they are chronic in nature.

New Daily Persistent Headache

New daily persistent headache (NDPH) is a category which is poorly understood and is a continuing field of ongoing research. The defining characteristic of a new daily persistent headache is a daily, unremitting headache with a distinct and clearly remembered onset. This condition often occurs in individuals without a prior headache history; however, it can occur in those with a sporadic, episodic headache history given that there is an abrupt change to unremitting daily headache without cause. New daily persistent headache is defined by the ICHD-3 as a persistent headache with a clear definitive onset (often a specific date and time can be recalled) that has been ongoing for at minimum 3 months [1].

The characteristics and associated symptoms, when present, are variable for NDPH. With more acceptance and recognition of new daily persistent headache, it has been seen that these patients may have features suggestive of either tension-type headache or migraine, so when multiple criteria are met, the default diagnosis remains new daily persistent headache based on the onset of the daily persistent headache. Individuals with NDPH more commonly had headaches that met the criteria for migraine headaches with associated features of nausea, photophobia, and phonophobia rather than tension-type headaches without any associated features. It has been suggested that individuals with NDPH with mostly migrainous features may have a form of prolonged status migrainous, which has important implications for treatment options [17, 18].

The pathophysiology is largely poorly misunderstood. There have been studies which identified viral infections, extracranial surgery, and stressful life events as triggers. However, in the same studies, 40% of patients had no known trigger. In another study looking for a trigger for new daily persistent headache, it was found that 23% of patients with chronic headaches had new daily persistent headache. Factors in this study that were found to be associated with the onset of new daily persistent headache included febrile illness, head trauma, and surgical procedures. This study highlighted that pediatric patients with or without a previous headache

history can abruptly transform into having a chronic daily headache syndrome. While etiology and triggering events have been hard to identify in NDPH patients, what has been suggested is that NDPH may be more prevalent in pediatrics, specifically adolescents, as compared to adults. Additionally, NDPH appears to be more common in boys as compared to girls. Whether there is something that truly sets the pediatric population apart from the adult population that leads to NDPH or if this is simply that those in pediatrics are simply recognizing NDPH and correctly identifying it as a diagnosis is yet to be determined. Potential risk factors for NDPH continued to be hypothesized with some consideration towards infections or postinfectious inflammation, traumatic head injury or other physical stress, or comorbidities such as autoimmune conditions as well as joint hypermobility [17, 19].

Part of the reason for this is the opacity of evidence and research in NDPH. Specifically, there is limited data that exists studying new daily persistent headache in the pediatric population; some of which that does exist has tried to parse out what separated NDPH from other chronic headaches, such as chronic migraine or tension-type headaches. One study looked at the clinical features of NDPH and compared it to those features of chronic tension-type headache and chronic transformed migraine headache [17]. While having headaches daily, the number of days of severe headache was significantly higher in those with NDPH as compared to chronic tension, and similar to that found in chronic migraine. Another study that looked at the characteristics of NDPH as compared to chronic migraine found that youth with NDPH experienced their first headache at a slightly later age than those with chronic migraine [18]. Additionally, individuals with NDPH were less likely to report photophobia as compared to those with chronic migraine, and also less likely to have a component of medication-overuse headache. The study also found that patients with NDPH seek medical help more quickly after initial onset of their headaches as compared to those with chronic migraine, likely because it is more commonly a new-onset unremitting headache that causes increased concern for the families [18, 19].

Evaluation of Chronic Daily Headaches in Pediatrics

The general topic of evaluation of a pediatric headache patient will be discussed in Chap. 6, but specific points that are relevant to pediatric chronic headache patients will be reviewed here. For children and adolescents with chronic migraine and chronic tension-type headaches, evaluation would follow for their episodic counterparts in general. This is because the headaches for this patients generally progress over time from episodic to chronic, and as such, unless concerning history features are reported or their exam is abnormal, especially any neurological exam abnormalities, workup would not routinely be recommended. There are always exceptions to the general recommendations regarding whether or not to perform a workup for a pediatric headache patient; ultimately, the decision to pursue an evaluation is

something that lies with the provider after seeing the child and discussing everything with the patient and their family.

The evaluation of a patient with chronic post-traumatic headaches may differ due to the fact that this type of chronic headache is triggered by a head injury. Currently, the general recommendations are that individuals who have sustained a minor head injury, as previously defined earlier in the chapter, do not warrant workup, including standard neuroimaging studies such as head CT scan or brain MRI, as long as there are not concerning features with the history nor the exam, especially the neurology exam [8, 12]. If an evaluation is not obtained at around the time of injury, this question of pursuing a workup may arise, especially if the headaches continue over time, down the road. What is important to remember is that with a normal exam, including a full neurological exam, and stable pattern of headaches, it is unlikely that an evaluation will yield findings that would lead to an alteration of treatment or new concern.

New daily persistent headache, similar to chronic post-traumatic headache, is looked at differently when it comes to considering an evaluation. Given the abrupt onset of headache that is unremitting, this type of chronic headache is typically evaluated with a workup that usually includes neuroimaging and laboratory evaluation. There is not a specific guideline when it comes to evaluating NDPH, so the evaluation is at the discretion of provider. When it comes to neuroimaging, brain MRI is the higher quality study so if possible would be the test of choice. Given that the differential for NDPH would include infection and tumor, neuroimaging with contrast should be obtained. Additionally, given that the etiology is unknown but many things have been suspected, a general laboratory evaluation is typically performed. Again, without specific guidelines and recommendations, the tests performed lie with the provider's discretion but typically include an infection screen, autoimmune screen, basic blood counts, and organ screen. The following are often obtained (not a comprehensive list): CBC, CMP, TSH, ESR, CRP, ANA, Lyme antibodies, and viral antibodies (CMV and EMV most often) [19].

Treatment of Chronic Daily Headaches in Pediatrics

The topic of treatment for the pediatric headache patient will be discussed in upcoming Chaps. 9 and 10 (Part IV), but specific points that are relevant to pediatric chronic headache patients will be reviewed here. The general principles of a multitiered approach starting at the foundation of lifestyle modifications followed by consideration of complementary and alternative therapies (to be discussed in detail in Chap. 9) are still where treatment should begin [13, 20, 21]. This is followed by implementation of prophylactic treatments, which could be nutraceuticals or medications (to be discussed in detail in Part IV), as well as advanced treatments such as available technology devices and procedures (to be discussed further in Chap. 12). Of note, what is similar to episodic and chronic headaches alike are the medications

themselves as those that will be discussed later are routinely used for prevention of headache, regardless of frequency or chronicity pattern [20–23].

Where the difference lies with chronic daily headache, children and adolescents are in the expectations for treatment. Unlike episodic headaches where the goal truly is to limit and space out the headaches as much as possible while also minimizing the severity and duration of individual headache episodes, the goal in treating chronic daily headaches is to maximize functionality. Given the amount of dysfunction and disability that accompanies chronic daily headache, the first step truly should be to try to get the children and adolescents back to as much of a normal routine and childhood as possible, despite the headaches. Once this has been achieved, then the goals and expectations can change to align more with that of treating pediatric episodic headache patients. As with the evaluation of pediatric chronic daily headache, there are always exceptions to the general recommendations regarding the treatment of chronic daily headaches. Ultimately, the decision on how to treat lies with the provider after seeing the child and discussing everything with the patient and their family.

A few notable aspects of treating chronic daily headaches are worth noting here as they are not necessarily applicable to episodic headache management. For example, given that there is more often moderate-to-severe disability with chronic headache, as compared to episodic headache, there is often a need to consider accommodations via a 504 plan or even an IEP, if warranted. While these types of programs allow collaboration between the child, the family, the providers, and the schools, caution should be taken not to let this progress to a point where more harm is being done than good, even though on the surface it seems to be in the interest of the child. Programs such as homebound schooling or home and hospital schooling should be avoided if at all possible. Removing the child from their normal environment and socially isolating often do more harm than good as the key to treating chronic daily headache is focusing on functionality. Additionally, the level of education is typically not the same with these programs, and they may lead to more stressors with the child and family as now the child is home all day, every day. Furthermore, rescue or acute treatments should be reviewed but with the focus to avoid frequent ongoing usage as medication overuse can be not only a common finding with pediatric chronic daily headaches but also an aggravating factor that may worsen their headaches and make preventative strategies less successful. Simple analgesics, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), are generally the first-line therapies but should be used with caution as they are often ineffective and could lead to medication-overuse headaches with regular use [15, 17].

Summary

As noted throughout this chapter, chronic daily headaches, while not typical, are quite problematic when they occur in the pediatric population. What makes this particular population tricky is that children and adolescents are not generally

complainers, so many of these individuals go unnoticed until there is marked dysfunction and disability related to the chronic headaches. Given this, it is critical to try and identify these patients as quickly as possible. However, that is only half the battle. The key is not only to identify those with chronic daily headaches, but also to treat them appropriately. This typically means a multitiered, and often aggressive, approach to try to combat the daily headaches as quickly as possible.

Return to Case #1

Following your exam, you discuss with your 16-year-old patient and her mother that what she is experiencing is chronic migraine based on her history. You also mention that there is concern for a medication-overuse component given her frequent ibuprofen usage. What is explained is that this is an unfortunate common progression for episodic migraine patients, as she was when she was younger. What is also reviewed is that it is important to work out a treatment plan as now that she is in a chronic migraine pattern, she is at a higher risk of high levels of disability including more days of missed school and poor academic performance. A multitiered approach is laid out to them, including avoiding overusing her NSAIDs or other acute interventions. In addition to limiting acute treatments, lifestyle modifications are reviewed and stressed as the foundation to the treatment plan. Complementary and alternative therapies are reviewed as an adjunct option, and amitriptyline is initiated as a prophylactic, after a normal EKG is obtained as TCAs can affect the QT interval. Follow-up is set for 4–6 weeks to see how things are progressing with the option to return sooner if her headaches are worsening.

Return to Case #2

Following your exam, you discuss with your 12-year-old patient and his parents that what he is experiencing sounds like chronic post-traumatic headaches based on his history. Furthermore, you note that he likely had a concussion with his head injury that occurred 6 months ago while playing soccer. You review general headache guidance and management as well as general head injury or concussion guidance. As his only symptom at this time is his ongoing headaches, you let the family know that the concussion seems to have resolved but has left him with his chronic post-traumatic headaches. Given his normal exam and workup when the injury occurred 6 months ago, you let his parents know that he does not need further workup for his headaches. What you do recommend is a consideration or a neuropsychological evaluation to see if he is having any lingering difficulties that may affect his schooling. You also suggest that depending on his school performance as well as his testing results, a 504 plan may need to be put in place for him to help him continue to heal while succeeding at school. Additionally, you recommend initiating a prophylactic medication for his headaches and select amitriptyline following a baseline normal EKG. Finally, you offer a referral to pediatric neurology headache clinic for consideration of additional treatments that they can offer such as possible nerve blocks to break the post-traumatic headaches or utilization of headache treatment technology

devices. Follow-up is set for 4–6 weeks to see how things are progressing with the option to return sooner if his headaches are worsening.

Return to Case #3

Following your exam, you discuss with your 10-year-old patient and his mother that what he is experiencing sounds like chronic tension-type headaches based on his history. It is explained to mom that tension-type headache is the most common primary headache seen and that it is not that unusual for progression into a chronic pattern. It is reviewed with mom that while episodic tension-type headache results in limited impact on functioning, chronic tension-type headache can impact daily function in school and social activities and as such it is important to have recognized this and to work to reduce his headaches before dysfunction and disability are noted. While he is having chronic tension-type headaches, he is not currently being affected much by his headaches. This, along with the fact that it is summer and therefore time before the next school year, it is decided to take a more conservative approach and to work on addressing potential lifestyle changes that may be contributing to his headache frequency, including adequate sleep hygiene, hydration, regular meals, physical activity, and medication overuse. Additionally, a headache calendar will be kept, and when they return in 4 weeks, it will be reviewed to determine if more aggressive management is needed with a daily prophylactic. It is stressed to mom that with chronic headaches, it is important to treat early as the longer they go untreated, the harder they are to treat in the long run, so if it is worsening, she is encouraged to return sooner to discuss next-step treatments for him.

Return to Case #4

Following your exam, you discuss with your 15-year-old patient and her parents that what she is experiencing sounds like new daily persistent headache (NDPH). You review that while this is noted in adolescents, it is an unusual presentation with abrupt onset and as such a workup is typically recommended with neuroimaging (even though her exam is normal) as well as screening laboratory evaluation. Additionally, the importance of initiating a multitiered treatment approach as soon as possible to try to help her get out of her daily pattern is discussed. The expectations for treatment are also reviewed with the initial goal to keep her functional as much as possible. As time progresses, the goals will adjust as she stabilizes and starts to improve to trying to reduce and resolve the headaches as much as possible. It is decided that a daily prophylactic will be initiated while the workup is obtained, and complementary and alternative therapies are researched in attempts to be more proactive in the treatment of her NDPH. Topiramate is initiated with titration every 2 weeks until target dose is reached. Follow-up is set for 2–4 weeks to review her workup and see how treatments are progressing in attempts to stay aggressive in her regimen as attempting to reverse her headache course as soon as possible is critical when dealing with NDPH.

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Part II
When to Worry and How to Evaluate the Pediatric Headache Patient

Chapter 6
The Clinic Visit: From History and Exam to When and How to Evaluate a Pediatric Headache Patient

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Case 1
A 13-year-old female with a past medical history of some recurrent abdominal pain in elementary school, but otherwise non-concerning and noncontributory, presents to your clinic for worsening headaches. The patient reports that she started getting headaches in the sixth grade, for which mom adds that it seemed to begin shortly after she went through menarche. Initially they were mild and nonspecific, but over the past year, the headaches have gotten worse and are now leading to an occasional missed day of school or extracurricular activities. The patient reports that she has about two severe headaches per month that are variable in location, described as aching, which last anywhere from a few hours to the rest of the day. Mom adds that when she has a headache, she has to stop what she is doing, including leaving school, and has to lie down in a quiet and darkroom as light and sound seem to bother her. The patient also notes that sometimes she has some abdominal pain and loss of appetite, and on 1 or 2 occasions in the last year, she has vomited with her headaches. There is no preceding warning sign of any kind prior to the onset of her headache.

Case 2: Secondary HA
A 9-year-old male with no past medical history comes in for worsening headaches. He was seen about 3 months ago for his well-child check where there was no mention of headaches and he had a normal exam. Mom says that the headaches started about 1 month ago and at first did not seem too bad but over the last week have

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progressed to near daily leading to a few missed days from school. His headaches are now lasting most of the day, as compared to a few hours when they started last month. He reports that the headaches feel like a pressure and aching around his whole head. He says that lights and sound can bother him sometimes as can his stomach. When asked, mom thinks that there have been a few nights recently where he has woken up sick with a headache and has vomited a few times overnight.

Introduction

It is easy to get overwhelmed when seeing a pediatric headache patient. Most families bringing their child for evaluation for headaches either wish to know whether they need to be concerned for a brain tumor or simply desire the knowledge needed to relieve their child's pain. Unfortunately, when either of these has been an ongoing concern by parents, loved ones, or even the patient themselves, the clinic visit can be a very daunting experience for all involved, including the provider as they are tasked with not only obtaining the information to help decide how to proceed with their patient, but also helping everyone present feel assured that everything is going to be okay. This is the hard part—while in most instances this is true and reassurance can be provided, there are times where this is not the case and a more insidious cause is suspected. Most have already been on the Internet, talked to friends and family, and tried over-the-counter medications, and a substantial number will have even tried homeopathic treatment options.

As with most conditions in medicine, a good history and exam are not the only place to begin but also the crux of how to address a pediatric headache patient and their family. The reason for this is that in the majority of cases, all that is needed by the provider to make a diagnosis and formulate a treatment plan is the history and exam. When that is not enough, there are evaluation tools that can be implemented to better assess the headaches, including referral to a specialist (pediatric neurology or headache medicine specialist). The focus of the provider should be directed at making a diagnosis of the most common primary headache disorders: migraines and tension-type headaches. However, when this is not the case or where there is a concern for a secondary headache, further steps are necessary. Here, not only will how to construct a headache clinic visit be discussed, but so will how to handle those times where common primary headaches are not suspected.

The Clinic Visit: History

A thorough yet directed headache history will allow the provider to save time and prevent unnecessary testing when evaluating a child with a chief concern for headaches. While this may sound like a straightforward simple task, it is harder than initially thought for a variety of reasons. One key confounding factory is that in

pediatrics, it may not always be possible to obtain a full reliable history from the patient, especially the younger the patient. While it would be nice to think that this only applies to young children, this can also be the case in older children and adolescents as well. In such cases, one of the biggest keys to success is working to build a rapport with the patient, young or old, as well as with the parents or caregiver as they may be called on to help round out the history. Where this becomes problematic is that to achieve a quality trusting provider-patient bond takes time and time is not always a luxury that is afforded to providers, especially in primary care. What works in the favor of the primary care provider is that hopefully with continuity of care, the beginnings of a good provider-patient/family relationship have already been forged. What also helps foster this bond is encouraging the child, regardless of age, to actively participate in their healthcare and be an equal participant going forward.

There are many ways to help create an environment that is patient centered so that a trusting and fruitful relationship can be created to better achieve a full, yet efficient, headache history from the patient and their loved ones. This may begin even before the visit as many pediatric providers will try to arrange the clinic space so that the child is seated closest to them. Another key is to focus on the patient from the beginning, rather than as an afterthought. By starting with the child, a sense of importance and power can be conveyed to them that they may not be accustomed to, and as such they may be more willing to engage earlier in the visit. By encouraging the child to express in their own words their headache history, the correct diagnosis is more likely to be made in a more timely manner.

Even when the patient is younger or not able to tell story verbally, there are ways to incorporate the patient in a meaningful way. In these cases, a child's self-portrait while having headache could be utilized to help establish a headache description and thus a more accurate headache diagnosis. Utilization of a child drawing to help distinguish migraine versus nonmigrainous etiology headaches is substantiated in the literature and can be easily implemented in a clinical setting such as when the parents or caregivers are providing history to the provider [1, 2].

Another strategy to help with a pediatric headache visit ahead of time is to, when possible, ask whether the patient or family maintain a headache diary. This could be conveyed when making their appointment to be seen. Of note, as most primary providers will see children in a timely manner when there is a new concern, including headache, there may not be sufficient time to create a prospective diary. In this situation, a prospective diary should be encouraged to be started, but also a request could be made to try to put together a retrospective diary to be able to provide as much information as possible at the time of the headache visit. Of note, diaries can be kept as a true diary, log, or calendar or even through various applications that are available for devices and smartphones. While there are countless items that can be documented in headache diaries, the goal with a headache diary should be to quickly, with as little burden as possible, record helpful information without too much minutia that can make the diary entry hard to navigate. Table 6.1 provides suggestions that should be included in an ideal headache diary. This could be simplified further, based on the patient, as it is more important to have some information rather than

Table 6.1 Pediatric Headache Diary

Date and time of onset of the headache, location of the headache, severity of pain, quality of pain, possible preceding triggers (specific foods, skipped meals, poor hydration, illness, sleep changes, weather changes, menses, etc.), associated features (light and sound sensitivity, changes in appetite, nausea, vomiting, etc.), duration of symptoms (headache and associated symptoms)
How was the headache treated (over-the-counter medications with doses, prescription medications with doses, hydration, eating, rest, sleep, homeopathic treatments, complementary therapies, etc.)
In retrospect, are there any premonitory symptoms prior to the headache starting? Are there any behavioral or mood changes prior to the headache starting? (Try to establish aura or prodrome.)
Was there any associated disability or dysfunction related to the headache or associated symptoms (missed school, missed family activities, missed extracurricular activities, missed work, inability to perform daily activities or responsibilities, etc.)?

none at all. In the most simplified version, headache frequency along with whether treatment was implemented and the presence of any dysfunction or disability should be recorded.

Once it is time for the visit itself, the goal is to make an accurate and correct headache diagnosis to the best of your ability. In doing so, the question as to whether the patient's symptoms can be attributed to a primary headache disorder or a secondary one must be answered. What seems to be a simple task on the surface can be more daunting than the first thought, especially when the history is hard to obtain. As with any other concern in pediatrics, history and exam are the keys to achieving this.

As a reminder, when the pediatric headache visit begins, it is recommended that the focus be on the child rather than the parents or caregivers. Any child that is developmentally able to communicate should be encouraged to answer as many of the questions regarding their headaches as possible. In general, expectations should be raised accordingly based on child's age, with older children providing majority of the history during visit. It is worth explaining to the child that there are no wrong answers and that it is more important that they use their own words to describe what is going on rather than trying to say the right thing or what they think others are looking to hear. Additionally, letting the child know that those who are with them for the visit will assist with any questions they cannot answer may help provide reassurance to the patient. Reassuring parents at the beginning of the visit that their concerns and questions as well as any additional history they would like to provide will be addressed after obtaining the patient's history will help keep the visit focused yet efficient.

In working toward making the correct headache diagnosis, it is wise to put aside any preconceived notions or expectations and rather focus on if the child is sick or not sick, and whether he or she is worried or not worried. In doing so, it could also be looked at as a question of does the child have a more common primary headache such as tension-type headache and migraine or not. This is because the crux of gathering the headache history is to determine if there is a concern for secondary headache and as such a need for further evaluation. Primary headaches, including

Table 6.2 Pediatric migraine diagnostic criteria [3]

A.	At least 5 attacks fulfilling B–D
B.	Duration 2–72 h
C.	At least 2 of the following 4:
	(a) Unilateral or bilateral
	(b) Pounding/throbbing pain quality
	(c) Moderate or severe pain intensity
	(d) Aggravated or avoidance of routine physical activity
D.	At least 1 of the following 2 (associated symptoms):
	(a) Photophobia and phonophobia (may be inferred)
	(b) Nausea and/or vomiting
E.	Not better attributed to another diagnosis/concern/explanation

Table 6.3 Pediatric tension-type diagnostic criteria [3]

A.	At least 10 episodes of headache occurring on <1 day/month on average (<12 days/year) and fulfilling criteria B–D
B.	Lasting from 30 min to 7 days
C.	At least two of the following four characteristics:
	1. Bilateral location
	2. Pressing or tightening (non-pulsating) quality
	3. Mild or moderate intensity
	4. Not aggravated by routine physical activity such as walking or climbing stairs
D.	Both of the following:
	1. No nausea or vomiting
	2. No more than one of photophobia or phonophobia
E.	Not better accounted for by another ICHD-3 diagnosis

tension type and migraine, as well as some commonly seen secondary headaches were discussed in previous chapters. While these will not be reviewed in full details, it is worth recalling the diagnostic criteria as this is critical to gathering a complete headache history and making the correct diagnosis (see Tables 6.2 and 6.3).

When constructing the pediatric headache history, it is important to remember that a quality headache history is taken rather than given. As such, it is important to keep in mind a checklist of questions in order to avoid missing key aspects of the headache history. While there can be much debate on exactly what questions are relevant to obtaining a full headache history, the most sited references for obtaining a headache history are by Dr. David Rothner and Dr. Paul Winner in 2001 and modified by Dr. Joseph Dooley in 2009 [4, 5]. Questions that should be asked and answered when seeing a pediatric headache patient include the following (of note, this is not a definitive all-inclusive list as each patient's story may trigger other pertinent or relevant questions; additionally, each individual provider may have additional questions they find relevant or helpful when seeing a pediatric headache patient):

Pediatric Headache History Questions

1. When did the headache begin? Chronic headaches are unlikely to reflect intracranial pathology. New-onset and or progressively worsening headaches are more likely to be due to a possible secondary cause such as a space-occupying lesion and as such typically warrant further evaluation with neuroimaging.
2. How did the headache begin? Look for precipitants, such as head injury, illness, other medical or neurological conditions, or stressors, including family or social.
3. What is the temporal pattern of the headaches? Intermittent headaches separated by intervals of well-being are most likely to be primary headaches such as tension type or migraine. Progressively more frequent headaches with escalating intensity are more likely to reflect a secondary process and as such require further investigations.
4. What is the headache frequency? Primary headaches tend to occur more intermittently, but even these can have a chronic version as noted in previous chapters. Generally speaking, migraines, especially earlier on in their presentation, tend to occur weekly or even less often. Tension-type headaches may occur more frequently than migraines, even from the onset, as they are often seen several times per week or more. Other headache subtypes in childhood, such as cluster headache or NDPH, may have their own unique pattern, occurring in clusters followed by long periods of headache freedom or constant daily from the onset, respectively. While both cluster headaches and NDPH are primary headaches, given their unique and less typical presentation, these subtypes are often, at a minimum, considered for further evaluation.

Let us consider Fig. 6.1 when considering questions 3 and 4. Most patients that come for evaluation for headaches will be represented by the blue line.

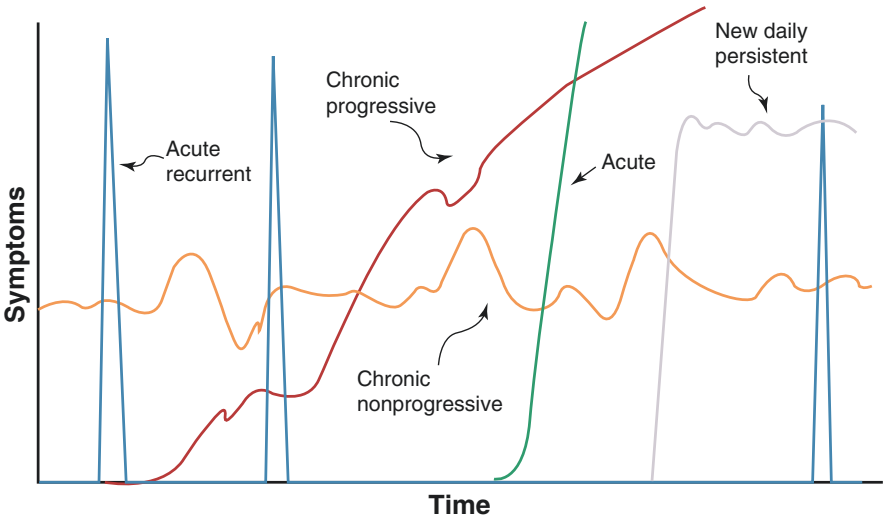

Fig. 6.1 Common headache patterns [11]

These individuals will have occasional headaches with intervals of being headache free. Most patients with an episodic headache pattern can and should be able to be managed in the primary care setting. Any individuals with a baseline headache pain on a daily basis represented by the yellow and purple lines or those with an escalating pattern represented by the red line should be considered and likely evaluated for a secondary cause of headaches. Providers should strongly consider referring these patients to a child neurologist or headache specialist for further evaluation.

5. How long does the headache typically last? Keep in mind that the ICHD-3 diagnostic criteria for various headache subtypes often include headache duration. However, it is also important to remember that duration includes the time of onset to next time normal, so, for example, if a patient lies down to sleep with a migraine, the timing would include the time sleeping for duration of symptoms. Additionally, not all patients will fall perfectly into a particular diagnostic criterion, especially in pediatrics. This is often true when considering headache duration as many pediatric migraine patients, for example, will note that their headaches will not last for a full 2 h. This could be due to treatment, patient or parent recall, or other countless factors. This reiterates the importance of keeping an accurate headache diary going forward.
6. Do the headaches happen at any particular time or circumstance? Headaches that occur at night or in the early morning are more likely to reflect increased intracranial pressure (ICP); however, primary headaches such as migraines may also occur at night. There are also subtleties regarding timing that are worth teasing out when taking a history. For example, does the headache wake the child from sleep or does the headache occur upon awaking or shortly thereafter? Children with primary headaches may describe waking with or developing a headache shortly after waking, especially if they had gone to bed the night before with an untreated headache. Of note, other considerations in children with recurrent morning headaches should include questioning regarding sleep concerns as sleep disorders, such as sleep apnea, often lead to morning headaches; when there is also a history of concurrent bruxism, temporomandibular joint dysfunction should also be considered. This contrasts possible secondary headaches with signs of increased ICP, which often awaken the child from sleep overnight or in the wee hours of the morning (this is often accompanied by associated symptoms such as vomiting). Occasionally, headaches can occur exclusively in one situation or circumstance (e.g., school, dietary changes or hunger, dehydration, sleep changes, menses, or changes in weather). When this is noted, there is generally less concern for secondary headache; focus can often be changed to discussion with the patient and loved ones as to how to best address the trigger and treat accordingly.
7. Is there an aura or prodrome? Children with migraines may be able to describe or draw their aura. Parents may predict a headache or migraine hours to even days before it occurs because their child may also show a prodrome of lethargy, mood change, thirst or food cravings, yawning, or pallor.

8. Where is the pain? Migraine is bifrontal in more than 55% of pediatric patients but can be unilateral, especially in older adolescents (as is typically the case with adults), as well as can be seen occipital in location, especially with certain subtypes such as migraine with brainstem aura [6]. Tension-type headaches are usually more diffusely located. Regarding location, it was once thought that occipital headaches as well as persistently unilateral headaches were more likely to occur in children with secondary headaches [7, 8], but further evaluation did not bear this out. As such, occipital location, which was once thought to be a red flag regarding pediatric headache, has become something that should be considered in the greater context rather than an automatic decision maker to warrant neuroimaging [1, 9]. For those with persistently unilateral headaches, this too should be taken into greater context with the entire history before deciding if additional workup is warranted.
9. What is the pain like—quality and intensity? Quality of pain may be suggestive of what type of headache is occurring, but not always. For example, migraines are typically thought to be throbbing or pounding, whereas tension-type headaches are thought to be pressure- or squeezing-like. However, nearly a quarter of adolescent migraine patients will describe their pain as different quality, often pressure-like [6]. An inability to describe the pain is more significant than the actual choice of adjective as historical concepts of pounding equating to migraine and band-like equating to tension type are probably inaccurate. Depending on the patient, offering choices may help determine the quality of pain, but be careful not to lead the patient to a particular answer. If choices are going to be provided, please ensure that there are several, varying choices that span a variety of headache subtypes. When considering the severity of pain, it is important to remember that while severity may suggest a particular headache diagnosis as it is noted in several criteria within the ICHD-3, it does not necessarily help in identifying a potential serious cause of headaches [3].
10. Are there associated symptoms? Migraines, per the ICHD-3 criteria, must be accompanied by at least one associated symptom (see Table 6.2). The list of associated symptoms may include, but is not limited to, nausea, vomiting, anorexia, photophobia, phonophobia, vision changes, dizziness or vertigo, osmophobia, mood changes, and cognitive concerns. Remember that while there are a multitude of possible associated or reported symptoms with pediatric migraine, only a few are part of the diagnostic criteria. When some of these symptoms present preceding the migraine headache, it likely is suggestive of an aura. Other headaches such as trigeminal autonomic cephalalgias (TACs) must also be present with associated symptoms (see Chap. 4 for details). Associated symptoms become concerning when they occur out of proportion to the headache. For example, vomiting, especially recurrent episodes, without accompanying nausea is suspicious. Additionally, when symptoms persist beyond the headache or if the associated phenomenon is persistent from one headache to the next, thought should be given to a possible underlying pathology.
11. What does the patient do during the headache? What a child does when a headache begins is often very informative. Those with migraines will usually inter-

rupt their activity as exacerbation by routine physical activity is one of the diagnostic criteria. Furthermore, many migraine patients will seek refuge in a quiet and darkened bedroom as light and sound are typically aggravating during a migraine [3]. Conversely, children with tension-type headaches will often be able to carry on with their activities, especially if it is something they are enjoying such as playing or watching television.

12. What makes the headache better and worse? Alleviating factors can be wide ranging from conservative measures such as hydration, eating, quiet, dark, or sleep to more targeted treatment with medications, both over the- counter and prescription, or other interventions. Details on medication use can provide insight into both the headache and the patient's and family's preferences for headache management. Many headache patients report using recurrent doses of medication (sometimes the correct age- and weight-based dose and sometimes not) despite their lack of benefit. This not only is ineffective but can even worsen the situation by possibly leading to medication-overuse headaches. The timing of treatment is also important to gage as many pediatric headache patients, as well as their families, try to wait out the headache before treating, thus delaying treatment that may have been more beneficial sooner. Aggravating factors or triggers (see question 6 above) are countless. Identifying these may not only help lead to a specific diagnosis and treatment as eluded to above, but also be used in identifying a potential underlying concerning etiology. For example, those with increased ICP will often find marked discomfort on lying down but possible improvement on standing up. Conversely, headaches due to low ICP are usually worse on sitting or standing up but improve with lying flat.
13. Are there symptoms between headaches? Patients with primary headaches such as migraine or tension-type headaches are generally asymptomatic between headaches. Ongoing symptoms, such as forgetfulness, confusion, or other neurological signs or symptoms, may suggest an underlying secondary concern or etiology. When there has also been a history of a head injury, even if seemingly minor, a possible concussion (mild traumatic brain injury (TBI)) must be considered and appropriately evaluated (while the specifics are out of the scope of this text, it is important to be aware of this and proceed with caution given the significance of head injury and concussion).

    In the setting of chronic daily headache, it can be difficult to tease out what are the associated symptoms of the headaches versus what are lingering symptoms between headaches. Unfortunately, the more long standing the headaches are and the more chronic they become, the more likely it becomes that the patient will get tired from their headaches and may start to have comorbidities such as mood changes and possible depression stemming from their chronic pain. Additionally, they may have more difficulties performing at their typical levels in all aspects of life (school, family, social/friends, extracurricular activities, work, etc.).
14. Are there any other health problems present, especially any that began around the same time as the headaches? Children with other health concerns, including surgical history and recent immunization/vaccination, may experience head-

aches as part of their other medical condition(s) and/or procedures. When another concern was noted to begin or take place around the time the headaches began, consideration for secondary etiology of the headaches should be entertained and explored, if possible. This also applies to individuals who have had trauma or head injury as noted above in question 13.

15. Medications? Headaches may occur as an adverse effect to medications used to treat other conditions or to treat the headaches themselves. If this is suspected, the decision to adjust treatment versus continue but encounter headaches as a side effect is an important but tricky discussion to navigate as there is no right or wrong way to proceed in this situation. Here, it is critical to understand the views of the patient and parents toward medication and treatment as well as to try to determine the dysfunction and disability related to the associated headaches. Separately, quantifying the child's use of nonprescription or prescription analgesics and medications will identify those at risk for medication-overuse headaches. A medication history may also reveal exposure or possible ongoing use of a medication that may be associated with specific headache subtypes. Idiopathic intracranial hypertension is an example of such a subtype that has been linked to oral contraceptives, vitamin A, isotretinoin, tetracycline, and corticosteroids [3].
16. Is there a family history of headaches? Given the overall prevalence of headache, especially tension type and migraine, it is extremely likely that there will be a positive family headache history. In fact, a lack of a family history of headaches may be of even more concern. While a negative history does not necessarily warrant further investigation alone, it is worth considering depending on the rest of the history and exam. Furthermore, given the genetic factors seen with migraine (see Chap. 2), this may not only help with providing a specific diagnosis but also lead to possible treatment considerations. In these families, educational efforts and counseling should be directed toward all those in the family with headaches, especially if it is a family member who is living with the child.

    In addition to headaches, it may be worth asking if there is any known family history of connective tissue disease, hypermobility conditions, aneurysms, other neurological conditions, or even brain tumors. While these conditions do not always have a genetic connection, especially in the case of brain tumors (rarely inherited but can be if associated with autosomal dominant neurocutaneous disorder such as neurofibromatosis), when present, they always are in the mind of the parents and caregivers and can even weigh on the minds of the patient. By asking about such conditions, it opens the dialogue to delve into their concerns as well as provides a chance for the provider to educate and offer reassurance while also considering the need for further evaluation and workup.
17. What is the daily lifestyle? Asking and addressing the daily lifestyle of a pediatric headache patient may not only shed light on what may be contributing to the headaches but also provide an easily accessible treatment option that lies fully in the hands of the patient and his or her family. Asking about the following daily habits or routine is something that should be part of every headache

patient history as well as subsequent follow-up visits: sleep routine, hydration, diet (including caffeine consumption), activity/exercise, and day-to-day stress or anxiety. While these factors will be discussed in more detail in Chap. 9, a few points are worth mentioning as they relate to the pediatric headache history:

- Sleep: bedtime routine including electronics prior to bed, bedtime, sleep patterns, duration of sleep, any signs/symptoms/history of sleep disturbance, including sleep apnea.
- Hydration: amount of non-caffeinated liquids consumed daily and urination patterns (color, frequency, approximated volume). Amount needed will vary for each patient based on various factors including, but not limited to, age, weight and height, amount of activity, season and weather (including humidity), and other medical factors (illness, medications, menstrual cycle). It is generally recommended that an individual have 6–8 good and relatively clear urinations a day to suggest adequate hydration status (* this is a suggestion and there are too many variables to review in detail here, but this would represent a good starting point to target for most patients).
- Diet (including caffeine consumption): having 3, relatively well-balanced, meals per day, at minimum, is recommended to help maintain normal metabolism and brain energy throughout the day. Additionally, avoiding excessive caffeine on a regular basis is also recommended. Maintaining a healthy weight is also worth mentioning, and while there are many factors that contribute to this, diet is often at the center of consideration with regard to a healthy weight.
- Activity/exercise: regular cardiovascular exercise or activity is intertwined with headaches; frequent (daily is recommended but may not be a reasonable or achievable goal for some) exercise and activity can help with not only headaches, but also sleep, weight, and even diet and hydration.
- Daily stress or anxiety: generally speaking, the more stress and anxiety that are present, the more headaches are to be expected and conversely, with a reduction in stress and anxiety headaches, often demonstrate a reduction as well.

18. Treatments tried to date? This can include any abortive/acute/rescue treatments that may have been tried including over-the-counter, prescription, and homeopathic/natural/holistic options. Additionally, any preventative treatments should be inquired about including any lifestyle modifications already made, nutraceuticals, or prescription medications. Complementary and alternative options should also be asked about as well as any potential devices/technologies or procedures that may have been implemented to try to help the headaches. Treatments will be discussed in subsequent chapters in more details.
19. Any workup, evaluation, or other consultation with regard to the headaches? It may be worth discussing with the patient or family if they have seen any other providers for the headaches and if any testing (imaging, laboratory, or ancillary workup) has been obtained. If so, it is worth delving into what has already been done to both determine if there is information already obtained regarding the

headaches and prevent repeating the same evaluation that has already been pursued.

20. What do you think is causing the headaches? This is usually a very valuable question. Some children will identify a particular stressor of which the parents are often unaware. Both children and parents are also afforded the opportunity to discuss their fears of underlying pathology. A number of families will demonstrate a remarkable misunderstanding of the potential causes of their child's headaches—for example, many believe that the headaches are caused by chronic sinusitis; however, there is no evidence to support chronic headaches as a result of chronic sinusitis [5, 10].

Remember that the key to seeing a pediatric headache patient is to make an accurate and correct diagnosis. The questions above will help you accomplish this through obtaining a very detailed, yet focused, headache history. Through obtaining this full history, you will, by default, remove any possible preconceived thoughts allowing you to determine if you are worried or not worried. Another way to assist in determining if the child is sick or not sick, and thus helping you decide on whether or not further evaluation, workup, or consultation is warranted, is to consider if potential red flags that may be present with pediatric headache patients are present or not. Additionally, it can be helpful to compare common primary headache features to those of secondary headaches as another way to get at the question of does the child have a more common primary headache such as tension-type headache and migraine or not.

Table 6.4 reviews pediatric headache red flags, and Table 6.5 compares primary headache characteristics to secondary headache characteristics. Of note, not all items listed in Table 6.4, red flags, necessarily indicate a definitive secondary headache or a requirement for further workup. Rather, these are items that may be

Table 6.4 Pediatric headache red flags

• *Age of presentation*[a]
• Explosive new-onset and/or worst headache of life
• Significant, abrupt changes in patient's headaches
• Early-morning or overnight headaches (awakening from sleep), especially when reoccurring on a frequent or progressive basis
• Early-morning associated signs/symptoms, especially those commonly seen with increased intracranial pressure
• Steady progression of headaches
• Worsening with straining (Valsalva) or position change
• Presence of other simultaneously developing neurological concerns such as seizure, movement disorder, cognitive or mental status changes
• Underlying neurocutaneous syndrome or other systemic illness/conditions
• Mood, school/work performance, and/or social/family interaction changes
• Abnormal neurological (including funduscopic) exam findings

[a]Age is more of a "yellow" flag rather than red as there is no specific age reported when worries should arise. Rather, when a patient is younger than the age that you are able to typically obtain a reasonably reliable history, you may need to consider this as a warning sign or reason to pursue additional evaluation. This often correlates to somewhere between 3 and 6 years of age

Table 6.5 Primary vs. secondary headache characteristics

Historical features	Primary HA	Secondary HA
Length of illness	Chronic, >6 months	Acute, <6 months
Pattern	Recurrent or daily	Progressive
Location	Frontal, lateral	Posterior
Quality	Throbbing, pressure	Pressure
Time of day	Anytime	Overnight or early AM
Frequency/duration	Variable/hours-days	Constant
Nausea/vomiting	Nausea >> vomiting	Vomiting
Visual aura/diplopia	Aura	Diplopia
Photo/phonophobia	Common[a]	Less likely

[a]Photophobia and phonophobia are hallmarks of migraine, but they can also be seen, individually or collectively, in other primary headaches

suggestive of a possible secondary headache and should be taken in context while considering the full history and exam when determining the likelihood of a concerning underlying etiology. Additionally, the list of common primary and secondary headache characteristics seen in Table 6.5 is more of a broad general representation rather than definitive concrete findings. While this table can help differentiate between primary and secondary headaches, it is important to remember that primary characteristics can be seen in secondary headache patients and vice versa. Ultimately, overall clinical judgement regarding a pediatric headache patient, which should include the full history, red flags, consideration of common primary versus secondary headache characteristics, and physical exam, is what will determine not only the differential diagnosis but also the subsequent need for further investigation.

Again, when seeing any pediatric patient, the key is to obtain a thorough, quality history that tells a story to allow for proper diagnosis and decision-making on where to go next. This holds true with pediatric headache patients as it is critical to gather the above information so that a correct diagnosis can be established along with deciding whether additional evaluation is warranted along with crafting a treatment plan. The challenge remains how to do this in a timely fashion given the constraints that are placed nowadays on primary care providers. By familiarizing yourself with recommended headache patient questions, as laid out above, and consistently obtaining this history, what once seemed like a daunting task can be achieved in a timely manner and confidently so that parties of the pediatric headache visit can be satisfied. However, this is only the first step in the pediatric headache clinic visit as the physical exam is just as important as is the decision on whether further evaluation is necessary or not.

The Clinic Visit: Examination

Just as with the history, the physical exam is critical for every pediatric headache patient. While the complete physical exam, including a full neurological examination, can often seem like an overwhelming task, with practice, repetition, and time,

it does not have to be. In fact, through these measures, it can be done confidently and quickly while allowing reassurance for not only you as the provider, but also the patient and their loved ones. The key to the physical exam is to assess whether the patient is sick or not sick. This fundamental evaluation begins even before the physical exam is performed. Through observation, determining if the child is sick or not sick starts the moment they enter the clinic setting and carries on throughout the entire clinic encounter.

As with any visit, vital signs, including height, weight, temperature, blood pressure, and heart rate, should be obtained. While this may seem somewhat mundane, vital signs can lead to an underlying etiology for the headaches. Up to 30% of acute headaches can be due to a viral infection [12]. Plotting a patient's weight will help determine if there is any concern for nutritional causes for headaches including failure to thrive or excessive weight gain that can be seen as part of a bigger concern, such as an underlying endocrine or pituitary concern as well as with certain headache subtypes like idiopathic intracranial hypertension. Additionally, orthostatic vital signs should be considered in any patient that is also noting any dizziness or lightheadedness, especially if upon position changes and being upright, as well as anyone whose comorbidities such as any form of dysautonomia are known or suspected.

When conducting an exam on a pediatric headache patient, it is important to start with a general exam. This would include a thorough head, eyes, ears, nose, and throat (HEENT) and neck exam with particular attention given to range of motion of the head and neck. Specifically, any evidence of meningismus, especially when combined with fever or sick symptoms, can be concerning for meningitis and should be evaluated emergently. Additionally, when looking at the head and neck area, the jaw area should be assessed looking for pain or symptoms suggestive of temporomandibular joint dysfunction such as jaw clicking or pain with opening and closing the mouth as this can often be associated with headaches. Furthermore, a dental exam looking for wear and tear may also be warranted when looking at the HEENT, especially if history reveals bruxism as this is often present with morning headaches.

Outside of the head and neck region, a good cardiac, respiratory, and abdominal or gastrointestinal exam should be conducted as abnormalities with these systems may be a sign of an underlying medical concern and cause to suspect a secondary headache. Additionally, a musculoskeletal exam should be done looking for any asymmetry or sign of injury that could explain or contribute to headaches. It is worth mentioning that many headache patients, especially those with chronic headaches, may have neck, shoulder, and upper back pain and stiffness that may be reproducible on exam. It can be difficult to determine which finding or symptom came first, but the history generally can provide the temporal course to help determine the timeline. A thorough, complete skin exam is also imperative to perform when seeing a new headache patient as headaches can be a presenting symptom for an underlying neurocutaneous syndrome. Should a neurocutaneous syndrome be suspected from the skin exam, further evaluation with a specialty consultation and imaging would typically be warranted.

In addition to the general physical exam, a thorough neurological exam, including funduscopic exam, is critical to perform when assessing a pediatric headache patient. The key to a high-quality neurological exam is repetition. By developing a certain order or pattern to the neurological exam, you will be able to perform a detailed comprehensive neurological exam in a timely manner without worrying that something was missed or forgotten. As with the general exam, the neurological exam starts from the time the patient enters the room by observing not only their physical actions but also their interactions with those involved in the clinic visit. Many aspects of the neurological exam can be seen, to varying degrees, simply by watching the patient while you are talking with them or their loved ones during the history; in fact, by observing them in a nonformal exam setting, you may be able to pick up on subtleties that may not be seen when they are focused on performing exam maneuvers.

The patient's mental status and overall affect should be noted, which typically can be ascertained during the history portion of the clinic visit, even with the younger pediatric patients. While there is an extensive list of possible findings within the mental status exam, the key things to observe include being able to communicate at an age-appropriate level (including verbal, nonverbal, and social aspects), demeanor and personality (especially if noted to be different than normal per patient or those accompanying the patient at the visit), and memory and cognition (generally obtained during the history; can include concerns related to school). Additionally, performing a mood assessment is crucial as headaches are one of the most common presenting symptoms of childhood mood disorders, including depression. This can be done through history or screening questionnaire.

Following mental status, cranial nerves should be assessed. While not all cranial nerves (CN), namely olfactory nerve (CN I), are routinely assessed, this is a critical portion of the exam as deficits here are often seen first and can signify an intracranial process. While a few key items will be discussed here, a full list of cranial nerves, their assessment, and findings/deficits to identify can be seen in Table 6.6. Of note, the funduscopic exam is often performed in conjunction with the cranial nerve exam as it assesses the optic nerve (CN II) through direct visualization. It is one of the, if not the, most important parts of the neurological examination and must be performed on every headache patient that presents for evaluation. Any funduscopic abnormalities can be a sign of increased intracranial pressure and warrant further evaluation, often on an urgent basis. When assessing the fundus, it is critical to view the optic disc looking for any blurring of the disc margins that would indicate swelling of the optic nerve. Additionally, assessing for venous pulsations is important and if seen is very reassuring that there is not increased intracranial pressure. What is difficult here is that there is a portion of the population who do not have spontaneous venous pulsations as part of their normal exam. Thus, seeing pulsations is again very reassuring but not seeing them is not necessarily a cause for concern. Unfortunately, many providers do not feel comfortable performing the funduscopic exam. It is recommended to perform (practice) the funduscopic exam on every patient seen, even those who do not have headaches, as this will help you be more comfortable with the exam and confident in the findings seen during the

Table 6.6 Cranial nerves

Cranial nerve	Function[a]	Examination[b]	Findings[c]
I = olfactory	Smell	Not typically tested	Not applicable
II = optic	Vision	Visual acuity, visual fields, funduscopic	Acuity changes, visual field deficits, optic nerve edema, lack of venous pulsations
III = oculomotor	Pupil constriction, eye movements	Pupillary light response, extraocular movements	Asymmetric pupil reaction, abnormal eye movements, reported diplopia
IV = trochlear	Eye movements	Extraocular movements	Abnormal eye movements, reported diplopia
V = trigeminal	Facial sensation	Touch in all branches bilaterally	Asymmetric or lack of sensation
VI = abducens	Eye movements	Extraocular movements	Abnormal eye movements, reported diplopia
VII = facial	Facial movements/ expression	Facial movements (wrinkle brow, frown, smile, show teeth)	Asymmetric or lack of facial movements/ expression
VIII = vestibulocochlear	Hearing	Hearing to finger rub	Asymmetric or lack of hearing to finger rub
IX = glossopharyngeal	Throat movements	Gag reflex (not routinely tested)	Absence or weak gag reflex
X = vagus	Soft palate movements	Voice quality, uvula movement (say "ahh")	Hoarseness, uvula deviation with saying "ahh"
XI = accessory	Shoulder shrug, head turn	Shoulder shrug and head turn to resistance	Weakness or asymmetry with shrug or head turn
XII = hypoglossal	Tongue movements	Observe speech, tongue movement	Slurred speech, tongue deviation

[a]Functions listed are not all inclusive as some of the cranial nerves may have additional functions; functions listed are those that are recommended to be assessed during the neurological exam
[b]Examination can include additional maneuvers to test alternate or additional nerve functions; examining some nerve functions can be achieved with varying techniques; some nerve functions and examinations can be combined into a single maneuver
[c]Common abnormal findings (this is not an all-inclusive list and other abnormalities may be identified)

exam. Until you are fully confident with your funduscopic examination skills, headache patients should be referred to ophthalmology for an exam. This would also hold true if the exam is unsuccessful for any reason or if there is any concern for possible abnormal findings, including lack of venous pulsations as this can be abnormal. The other key cranial nerve assessment to focus on when evaluating a headache patient is extraocular movements as abnormalities here are often one of the first findings to present when there is increased intracranial pressure or other intracranial process leading. Of note, remember that double vision typically arises from eye misalignment and/or abnormal eye movements, so pay particular attention

to this portion of the exam when diplopia is reported by the patient. When these, or other, cranial nerve abnormalities are identified on exam, the concern for secondary headache comes to the forefront and thus further evaluation should be obtained in a timely fashion.

The motor and sensory exam should also be performed as part of the comprehensive neurological exam. Remember that when assessing these areas, look at all four extremities so that left and right as well as upper and lower extremities can be compared for symmetry. For the motor exam, it is crucial to assess for signs of focal or asymmetric weakness. Pronator drift is an exam maneuver that can and should be used as part of the neurological exam as it identifies subtle motor deficits and asymmetries. Of note, the motor exam begins with observing the patient as they enter the clinic room and continues throughout the visit by monitoring their positioning, posture, and movements during the visit. This, too, holds true for the sensory exam as observing the patient throughout the visit can provide insight into some aspects of their sensory exam. It is worth noting that the sensory exam is the most subjective part of the neurological exam, but it is still important to assess for marked differences, asymmetries, and deficits. A few items that can help assess the sensory system are gross touch, pain (sharp) or temperature, and proprioception. Additionally, coordination should be evaluated as part of the neurological exam looking for ataxia or dysmetria. Performing finger-nose-finger testing or having the patient reach for objects in the room with each hand will help determine if there are any problems with coordination. Watching their positioning and truncal movements during the visit and exam is also important when assessing for ataxia. Romberg testing is often performed at this point of the neurological exam as a positive finding can point toward abnormalities with sensation and/or coordination. With the patient already standing for the Romberg test, gait testing can be performed next. This, too, starts from the time the patient enters the room but here as part of the formal exam typically includes heel, toe, and tandem gait. These maneuvers assess not only gait but also motor. The final part of the neurological exam is assessing deep tendon reflexes in the ankles, knees, wrists, and elbow. When testing, it is important to note the presence or absence of reflexes, any asymmetry between left and right, upper versus lower extremities, as well as the presence of clonus. It is important to remember that adolescent girls often have easily elicited brisk reflexes, and what is important to note is whether there are any marked asymmetries in that particular patient. Any evidence of motor or sensory abnormalities, coordination concerns, abnormal gait, or abnormal reflexes may be a concern and as such should lead to further evaluation.

Fortunately, most headache patients will have a reassuring, normal physical examination including neurologic and funduscopic examinations. Given this, the challenge is to stay focused and remain committed to performing a full, thorough examination on every headache patient as you never know when an exam abnormality may be found or a secondary headache may be present. Remaining consistent in your exam, reminding yourself to be cognizant of the sick (versus not sick), and knowing the abnormalities to be on the lookout for (see Table 6.7 for some of the more common physical exam findings of concern) will help you not overlook any concerning physical exam finding.

Table 6.7 Physical exam abnormal findings [4, 5, 13–16]

1.	Abnormal general condition (including, but not limited to, vital sign abnormalities, fatigue, loss of energy, mood or personality change)
2.	Growth failure including failure to thrive
3.	Precocious, delayed, or arrested puberty
4.	Impaired consciousness or mental status changes
5.	Abnormal funduscopic exam
6.	Cranial nerve palsies including abnormal eye movements, diplopia, and pupillary response
7.	Focal weakness or hemiparesis
8.	Sensory deficits
9.	Developmental regression
10.	Ataxia or new incoordination, balance concerns, or gait abnormalities
11.	Abnormal reflexes

Again, it is worth repeating that most pediatric headache patients will have a normal exam. In fact, when combined with a reassuring headache history, a normal physical exam should be extremely reassuring to not only you, as the provider, but also the patient and their loved ones. The vast majority of children with secondary headaches attributed to an underlying intracranial process will have at least one neurological exam abnormality (see Tables 6.6 and 6.7) with many patients having multiple abnormalities within the first few months of developing headaches, and by 6 months, essentially all of these patients will exhibit abnormal neurological exam findings [4, 5, 13–16].

Once the full headache history has been obtained and the complete physical exam has been performed, the next phase of the visit can begin, which entails the discussion with the patient and their loved ones with respect to the following: (1) what is the diagnosis, (2) where did the headache come from (etiology), (3) what additional evaluation is warranted, and (4) what is the recommended treatment (to be discussed in upcoming chapters). The first step is to make the correct diagnosis, which is achieved by combining the obtained history and performed physical exam with the knowledge of the headache classification criteria, as reviewed in previous chapters. The next question addressing the etiology is truly challenging as there is not a true cause for primary headaches, but rather contributing risk factors (again discussed in previous chapters) that may make headaches more likely in a given individual. When a secondary headache is suspected, this can be just as challenging to discuss, but for different reasons, as this means that there were concerning features in the history or on exam that may suggest an underlying etiology of concern. This leads to the third part of the discussion, which reviews the need for further evaluation.

The Clinic Visit: Further Evaluation

Fortunately, most pediatric headache patients do not warrant further evaluation. This is because most pediatric headache patients will have primary headaches, a non-concerning history without red flags, and a normal physical examination. For

those individuals where this is not the case, further investigation can include the following: laboratory studies, ancillary testing, neuroimaging, and referral or specialty consultation [14, 16]. Of note, there are certain primary headaches, such as NDPH, which were discussed in a previous chapter, as well as certain circumstances, such as progressively worsening or refractory cases, where further evaluation can or should be considered. Additionally, as a primary care provider, you will be faced with having to address the most common question from loved ones—that is, whether there is a need for any additional testing, especially brain imaging—even when there is no concern based on history and exam. When reassurance from your established relationship as their primary care provider, their non-concerning history, and their non-focal exam is not enough, there are guidelines from the American Academy of Neurology (AAN) and the Child Neurology Society (CNS) that have been in place since 2002, which address evaluating pediatric headache patients [17].

Specifically, the guidelines address the utility of laboratory studies, ancillary testing, and neuroimaging [17]. As mentioned above, the AAN and CNS guidelines established that if the child has a non-concerning history and normal examination and meets the diagnostic criteria for primary headache disorder such as migraines or tension-type headaches, there is little to no utility in performing additional evaluation with routine laboratory studies, ancillary testing, or neuroimaging. Even when further evaluation is warranted, laboratory studies are not typically part of those recommendations unless there is underlying concern for a general medical or metabolic process. Laboratory studies may be utilized in pediatric headache patients when certain medications are used as an ongoing headache treatment. Similar to laboratory studies, ancillary testing is not routinely considered as part of the further evaluation of a pediatric headache patient. Conversely, when concerns such as a central nervous system infection, increased intracranial pressure, and/or coexistence of seizures are present, ancillary testing is recommended and can include, but not limited to, lumbar puncture, cerebrospinal fluid analysis, and electroencephalogram (EEG) [14, 16, 17]. Additionally, certain ancillary tests, such as an electrocardiogram (EKG), may be utilized when certain treatments are initiated and maintained.

When considering further evaluation for a pediatric headache patient, whether it is based on clinical concerns or concerns raised from the patient and their loved ones, the topic that leads to the most discussion is neuroimaging. While neuroimaging does have a place in further evaluating a pediatric headache patient, it should be reserved for when there are true concerns raised from the history or exam. This is where the challenge lies, as many patients and their loved ones present for a headache clinic visit purely with the goal of receiving neuroimaging. As noted above, hopefully you are able to provide enough reassurance, when appropriate, that the patient's or their loved one's desire to obtain imaging is not necessary. When this cannot be done, or there is concern for a secondary headache, neuroimaging may be warranted. Table 6.8 notes reasons a provider may consider obtaining neuroimaging for a pediatric headache patient based on the AAN and CNS practice parameter [17]. Of note, these guidelines are not all encompassing. Each patient must be considered individually taking into consideration any concerning history, red flags, or abnormal exam findings, as well as the provider's clinical judgement.

Table 6.8 Practice parameter reasons to consider obtaining neuroimaging [17]

1.	Abnormal neurological examination
2.	Coexistence of seizures
3.	Signs or symptoms of increased intracranial pressure
4.	Atypical/concerning headache features or features that may suggest neurological dysfunction (e.g.: intractable vomiting, waking from sleep, unusual or rare associated features such as hemiparesis)
5.	Recent onset of severe headaches or steady progressive pattern
6.	Change in type of headache

Additionally, there are other factors that may be worth considering with regard to whether further evaluation with neuroimaging is needed. When the presentation is for the first or worst headache of life, imaging may be warranted. Clinical judgement is needed in this setting as this presentation can often be seen, especially in primary care. Age of presentation is another point of contention regarding additional workup as there are not definitive recommendations as to what age necessitates the need for further evaluation. A general consideration can be to pursue neuroimaging in patients who are too young to provide a history. This age may vary depending on the patient, the provider, the type of practice, and the time allowed for the visit but typically falls somewhere between 3 and 6 years of age. Furthermore, when headaches present in an immunosuppressed or immunocompromised patient or someone with systemic signs and symptoms, secondary headaches must be considered, and as such neuroimaging is often considered as part of the evaluation. Over the years, the location of the headache in a pediatric patient has also been a concern, especially when it was noted to be posterior or occipital in location. More recently, this has come into question and is no longer considered a true red flag that automatically warrants further investigation with neuroimaging. Instead, location of the pain should be taken in context with the entire history and exam when deciding if additional evaluation, including neuroimaging, is necessary [1, 9].

When neuroimaging is going to be obtained, be mindful of what imaging would be best in that particular situation. In general, magnetic resonance imaging (MRI) is the ideal neuroimaging modality as it provides more detailed imaging, is better for visualizing the posterior fossa, and does not expose the patient to radiation. The problem is that MRI is not available in all locations, takes longer to schedule leading to a delay in obtaining the imaging, and is a longer study so may require sedation or anesthesia with younger patients or those who cannot remain still for prolonged periods of time. The alternative to MRI is computed tomography (CT). CT imaging is often the test of choice in an acute situation as it is easier to obtain, is quicker, and is more readily available in more locations. The downside to CT is that the quality of imaging is less as compared to MRI, does not visualize the posterior fossa well, and exposes the patient to radiation. Of note, contrast imaging is recommended when there is suspicion of inflammatory or infectious etiology.

When to refer the patient to a pediatric neurologist or headache specialist should be considered as part of the pediatric headache clinic visit. There is no hard-and-fast

rule as to when a patient should be referred for specialty evaluation and care. In general, if at any time you, as the provider, or the patient or their loved ones, feels that it is in the best interest of the patient to seek specialty care, then that is the right time. This is especially true when despite your best efforts at reassuring the patient or their loved ones there remains an underlying fear or concern. Additional reasons to consider referral would include secondary headaches (especially if beyond the scope of your practice), rare or unusual primary headaches (especially if beyond the scope of your practice), refractory headaches, headaches in the setting of neurological comorbidities, or when the evaluation identifies an underlying concern. Ultimately, you will never be wrong to refer the patient to a neurologist or headache specialist if you are doing so in the best interest of the patient.

Summary

As noted throughout this chapter, a pediatric headache clinic visit can be very challenging. However, they can also be very rewarding for all, especially when you can provide reassurance for those who fear the worst. As with any pediatric patient or visit, the key remains the history and exam. While this, too, can be challenging, with structure and repetition, it can become just like seeing any other patient. By using the information above, a thorough, complete headache history and exam can be obtained in a timely fashion that will allow you to make the correct diagnosis, discuss their headaches, assess the need for further evaluation, and formulate an appropriate treatment plan. And when all else fails, there are specialists as well as guidelines and recommendations you can access to help with your pediatric headache patients and their families.

Case 1: Resolution

Once the history is completed, you perform her physical exam that is unrevealing, normal, or non-focal. Specifically, her neurological and funduscopic exams are normal. Following your history and exam, you are very reassured that your 13-year-old patient is having primary headaches, rather than a more concerning secondary headache. You discuss with your patient and her mother that her diagnosis is episodic migraine without aura. You are able to provide reassurance to both your patient and her mother. You are able to spend the rest of the visit reviewing a treatment plan that incorporates lifestyle review and modification where necessary. Additionally, you review the non-pharmacological approaches such as various types of therapies but let them know that with her current frequency of migraines, these may not be needed at this time. You review prophylactic treatments, including nutraceuticals, focusing on when it would be recommended to initiate one of these options. Given that she is having only 2 migraines a month, you, along with your patient and her mother, agree to hold off on starting a daily preventative but rather to see how conservative management helps over the next few months. You recommend an acute treatment plan initially with an NSAID and fluids but mention that a migraine-specific

abortive can be used, such as a triptan, if needed. You encourage them to track her migraines with a calendar and return for follow-up visit in 2–3 months, or sooner if her headaches are changing or worsening.

Case 2: Resolution

Once the history is completed, you perform his physical exam that is grossly unrevealing. Specifically, his neurological exam looked good, but you are not fully convinced that you were able to see sharp optic discs or venous pulsations on funduscopic exam. Following your history and exam, you are concerned that your 9-year-old patient may be having a secondary headache, rather than more benign primary headaches. You discuss with your patient and his mother that you are unable to provide a definitive diagnosis. You review your concern for possible concerning headaches due to an underlying intracranial process but let him and his mother know that you will be getting his workup and evaluation started today. Given his grossly normal exam, you decide to pursue an urgent outpatient evaluation rather than referring him directly to the emergency department. You refer him to see a pediatric ophthalmologist for a dilated eye exam, and you order an MRI brain with and without contrast, as you have a concern for possible intracranial mass. You let mom know that you will call to expedite these evaluations but that if he changes or worsens in any way, she should bring him back for an evaluation or take him to the local pediatric emergency department for evaluation. You review headache lifestyle recommendations but defer any prophylactic treatments at this time until his evaluation is complete. You tell mom that for his headaches, she can use acetaminophen or NSAIDs 2 or 3 times a week in the meantime if his headaches are bothering him. He is scheduled to return later in the week to review how he is doing as well as the results of his workup.

When he returns later that week, mom says that he is maybe a little better with working on drinking more fluids and getting to bed a little earlier. His exam is unchanged. He had his MRI completed and was normal without any contrast enhancement. His ophthalmology exam was also normal without evidence of any optic nerve edema. On further questioning, mom mentions that a few months back when his headaches started, he had fallen while playing with his sister and hit his head but since there was no loss of consciousness and he seemed ok she did not make much of it. She also says that over the last few nights since his prior visit, she has realized that he was going to bed with a headache without saying anything and then would wake up with a worsening headache. With a negative workup, a reassuring exam, and the updated history, you diagnose him with likely a mix of post-traumatic headaches and migraine, given the reported associated symptoms. You encourage them to continue to work on lifestyle modifications, review possibly considering physical therapy to help with his headaches, and recommend starting cyproheptadine to help with his headaches and sleep and continuing acetaminophen or NSAIDs for rescue up to a few times a week as needed. You schedule a 1-month follow-up but ask mom to update you in a few weeks with how he is doing, or sooner if there are any concerns or changes.

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Part III
Comorbid Concerns in the Pediatric Headache Patients

Chapter 7
Neurologic and Psychiatric Comorbidities in Pediatric Headache Patients

Ryan P. Williams

Case 1

A 13-year-old female with a no past medical history presents to the office today for her well-child yearly visit. During the visit, it is mentioned that she is having some new jerks and vocalizations that are more noticeable to mom as well as a few bad headaches a month. It is discussed with mom that she should return for a dedicated visit to review these new concerns. Basic lifestyle modifications, including sleep hygiene, were discussed as a few steps to start thinking about before they return next week for a follow-up visit.

When they return, the patient reports that she started getting headaches in sixth grade. This school year, her mother notes that she has had to miss a few school days due to her headaches. The patient reports that she has 2–3 headaches per month, which last for about 6 h. Her headaches are always associated with light and sound sensitivity, and on rare occasions, she reports nausea. She says that she has been treating her headaches with ibuprofen, which helps sometimes. Additionally, mom reports that over the last few years, she has noticed more episodes of eye blinking and little jerks of her mouth or head, and over the last year, she has noticed some throat clearing and sniffing even when it was not allergy season. The patient says that she does not realize that she is doing these things and they do not bother her or interfere with her daily life, including social functioning. Of note, when reviewing the patient's daily routine, it comes up that she does not go to bed until after midnight most nights as she is on her phone with friends but then has to wake up at 6:00 a.m. for school and is exhausted most days. Her exams, including neurological and fundoscopic exams, are normal.

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Case 2
A 14-year-old male with a past medical history of ADHD, which is poorly controlled on his current stimulant medication, presents to clinic for an ongoing headache. The patient reports that he started getting his headache a little over 3 months ago. He, nor his mom, can recall any inciting event other than he may have had a cold or virus a few weeks before the headache started. The headache is described as a holocephalic generalized pressure. The pain was mild at first but now is more moderate. He reports some mild light sensitivity sometimes, but generally it is just the headache. They have tried ibuprofen and acetaminophen without benefit. Mom also reports that she does not feel that his medication for his ADHD, which has not been adjusted in 2–3 years, is working. She became concerned when his report card came out for the most recent marking period and his grades had fallen in all of his core subjects. On further questioning, the only concern regarding his ADHD is due to his grades as mom has not noticed any issues with his focus at home or any other facet of his life. His exams, including neurological and fundoscopic exams, are normal. Mom also give you a Vanderbilt form from her and dad as well as a few of his teachers.

Case 3
A 17-year-old female with a past medical history of migraines, which were treated conservatively with lifestyle modifications and a rescue plan of ibuprofen and rizatriptan, presents to clinic for an increase in her migraines. Over this school year, she and mom have noticed that she has missed quite a few days from school even though it is virtual school due to the pandemic. The patient reports that she has about six "bad" headaches a week that last most, if not all, of the day. She reports that most of her headache days have light and sound sensitivity as well as nausea. When you ask her how she is doing overall, she begins to cry and does not want to talk. Mom notes that she has struggled with the pandemic becoming increasingly more withdrawn and isolated as time has progressed as well as seeming to be angry or upset most of the time, especially when discussing her schoolwork. Her exams, including neurological and fundoscopic exams, are normal.

Epilepsy and Migraine

Both epilepsy and migraine lead to significant morbidity and, in the case of epilepsy, rare mortality. The connection between these two neurological diseases has been hypothesized since the early days of neurology. In 1873, Liveing described "the intimate relations of megrim with the whole family of neurosal disorders of which Epilepsy is the type" [1]. The prevalence of migraine in childhood is higher than that of epilepsy (3–23% vs. 0.5–1%). Yet, various studies have shown that the rate of epilepsy in migraine patients and migraine in epilepsy patients is higher than that in the normal population. In looking at 400 children with epilepsy, Kelley et al. [2] found that 25% met the ICHD-II criteria for migraine. This rate is similar to the migraine prevalence of 8–24% found by Kim et al. [3] in all epilepsy patients

(children and adults). Toldo et al. [4] found that children with epilepsy had a 4.5 times higher risk to have migraines than to have tension-type headaches. When severe headaches are included alongside migraines, prevalence in epilepsy patients can exceed 35% (Centers for Disease Control and Prevention: Comorbidity in adults with epilepsy—United States, 2010. MMWR Recomm Rep 62: 849–853, 2013). The connection between these chronic diseases appears to hold for both "benign" childhood epilepsies (e.g., benign Rolandic epilepsy, benign occipital epilepsy of childhood, Panayiotopoulos syndrome) and lifelong epilepsy syndromes (e.g., juvenile myoclonic epilepsy) [2, 5].

As alluded to above, when investigating the relationship between migraine and epilepsy from the opposite direction, the connection is also apparent. A 1987 study showed the prevalence of epilepsy to be higher in migraineurs than non-migraine patients, 17% vs. 1% [6]. In fact, patients with migraines were noted to have a higher risk for epilepsy than tension-type headaches [4]. Thus, the relationship is often bidirectional [7].

Pathophysiology

Yet, entry into this relationship more typically starts with epilepsy than with migraines [2, 4]. This begs the question of how these factors relate on a molecular and/or genetic level. And indeed, a shared pathological basis between migraine and epilepsy has been hypothesized, with a prominent focus on ion channel mechanics. Sodium channels such as AMPA and NMDA have been implicated in the propagation of seizures and cortical spreading depression, respectively [8]. Mutations in specific channels (e.g., CACNA1A, ATP1A2, and SCN1A) can be seen in both patients with migraines and those with seizures [9]. A genome-wide linkage analysis of migraine phenotype in 38 families with Rolandic epilepsy showed evidence of linkage to migraine at 17q12-122 and suggestive evidence at 1q23.1-23.2, a known locus associated with FHM, type 2 [10]. Additionally, a case report by Costa et al. [11] showed a three-generation family with five patients having a novel ATP1A2 mutation on exon 19 with all five patients having migraine, four with FHM2.

The interplay between the function of these genes in epilepsy and in migraines, however, is complex. It is likely that the mechanisms of channel function work differently in seizure than in migraine and have different intrinsic or extrinsic triggers. Various studies have revealed that, in epilepsy patients, migraines can occur at several phases in respect to seizures. A study by Matlu [12] revealed that migraines in epilepsy patients typically occur interictally rather than peri-ictally. On the other hand, Mainieri et al. [13] showed a higher rate of migraine in the pre-ictal period in patients with both epilepsy and migraine. Duchaczek et al. [14] discovered that 40–60% of patients with epilepsy experience a peri-ictal headache—not necessarily migraine—sometimes during their epilepsy course. And another study showed that postictal migraine symptoms occur in 1/3 to ½ of patients with the Gastaut form of benign occipital epilepsy of childhood [15].

Migralepsy

To add to the complexity, there are reports of migraines appearing in an ictal fashion, a concept that has been coined "migralepsy" (c.f. [16]). The International Classification of Headache Disorders (ICHD 3-beta) includes the term "migraine aura-triggered seizures" requiring a migraine with aura and seizure to co-occur or for the seizure to occur within an hour of the migraine. A study of 4600 children with epilepsy showed 16 children with migraine-like manifestations of seizure. The majority (14/16) showed interictal epileptiform abnormalities (frontal, central, occipital, temporal) that continued through the migraine. Two patients showed epileptiform abnormalities (temporo-occipital, parieto-occipital) only during migraine [17]. Fusco et al. [18] described the case of a 9-year-old boy with a history of Rasmussen's encephalitis who, 2 years following disconnection surgery, developed migraine headaches that were shown to be consistent with focal occipital status epilepticus over the right hemisphere and resolved with IV diazepam.

Treatment

Given the comorbidity between epilepsy and migraine, fortunately, there are treatment options that can be helpful for both conditions. Anti-seizure medications such as topiramate and valproic acid are mainstay treatments for both conditions. Recently, there have also been reports of effective migraine prevention with levetiracetam [19, 20]. Clearly, evidence abounds that these two morbid neurological disorders are connected, and future research into the molecular and genetic pathophysiology will likely lead to more knowledge and potential treatments.

Migraine and Sleep Disorders

Poor sleep is a common complaint in childhood. Owens and Whitmans [21] revealed that 25% of children experience at least one type of sleep problem. Therefore, it is certainly not surprising that sleep dysfunction is also reported in children with headaches. Indeed, sleep problems are the most common comorbidity in pediatric headache [22]. These disturbances include insufficient sleep, restless sleep, difficulties falling asleep, nighttime waking, and daytime fatigue [23]. Importantly, these sleep complaints do not dissipate when factoring in common psychiatric comorbidities such as anxiety and depression [3]. Disordered sleep in the form of insomnia, restlessness, sleep-disordered breathing, and maladjusted sleep stages, among other issues, has the potential to exacerbate headache disorders [24, 25]. Interestingly, it is discontinuous sleep, not necessarily decreased sleep duration, that is implicated in decreasing pain thresholds [26]. However, while impaired sleep can exacerbate

headaches, the act of sleeping is typically an effective rescue strategy for migraine [27]. In this light, identification and management of sleep disorders are a necessary component of caring for children with headaches.

Pathophysiology

The basis for connection between sleep and headaches has been proposed to center on the role of the hypothalamus and brainstem. Mechanistically, disruptions in hypothalamic function involving the neurotransmitters dopamine and serotonin are hypothesized to be involved in both sleep and headache. Dopamine appears to be involved in the premonitory phase of migraine [28], and data from rats shows that dopamine can impact neuron firing in the trigeminocervical complex [29]. Dopamine is also an essential part of the sleep-arousal pathway via connections from the hypothalamus to the periaqueductal gray. Serotonin likely plays a role in both the interictal and ictal phases of migraine. Migraineurs have been shown to have decreased serotonin levels interictally with the release of intracellular serotonin being an early marker of migraine attack [30]. Sleep efficiency and amount of slow-wave sleep are decreased in migraine patients [31–33], and serotonin has a role in sleep-stage progression as well as in migraine [34]. Given its production within the brainstem, this fits along well with the noted dopamine connection.

In addition to the hypothalamic role, the recent discovery of the glymphatic system has led neuroscientists to investigate its role in the migraine-sleep connection. The glymphatic system appears to function mainly during sleep. Schain et al. [35] studied mice and showed that induced cortical spreading depression leads to decreased glymphatic flow from temporary closure of the perivascular space. Given its nocturnal activity, it has been hypothesized that patients with chronic migraine may lose the restorative functions of sleep secondary to decreased glymphatic flow and accumulation of toxic metabolites typically eliminated during sleep [34, 35].

Insomnia

Within the sleep disorders, insomnia is the most commonly reported and includes difficulties falling asleep and maintaining sleep [36]. Patients with migraine have a higher likelihood of reporting insomnia than controls [37]. The relationship is bidirectional. Boardman et al. [38, 39] showed that insomnia preceded and predicted both new-onset headache and migraine exacerbation. From the other direction, Odegard et al. [40] revealed that migraine also predicts insomnia. Fortunately, treatment of insomnia with a specific cognitive behavioral therapy designed for insomnia (CBTi) has been shown to be effective both in improving sleep efficiency and decreasing headache frequency [41]. Additionally, sleep-promoting agents such as melatonin help with sleep-wake regulation as well as headache prevention. Patients with

migraine and cluster headaches have been shown to have decreased melatonin secretion nocturnally [42, 43], and treatment with melatonin has shown some efficacy [44]. Studies of melatonin in children with tension-type and migraine headaches [45, 46] have shown reductions in headache frequency, duration and disability.

Sleep-Disordered Breathing and OSA

Sleep-disordered breathing such as snoring or, more critically, obstructive sleep apnea (OSA) is also noted to be a problem in headache patients. Snoring, specifically, is a risk factor for transformation into chronic headaches [47]. Vendrame et al. [32] looked at polysomnographic findings in children with headaches and found that sleep-disordered breathing was more common among children with migraine and nonspecific headaches than chronic migraine (56.6% vs. 54% vs. 27%). There is an argument in the literature, however, over the significance of the connection between OSA and headaches and whether there is truly increased prevalence of OSA in migraine patients. In looking at OSA patients, Provini et al. [48] identified a variable headache prevalence of between 18 and 60%. A different study of 235 OSA patients found that 20% reported headaches upon awakening with headache semiology consistent with migraine (25%), tension headache (40%), cluster headache (2%), and nonspecific headache (33%) [49]. On the other hand, a more recent investigation by Vgontzas and Pavlovic [34] indicated that the rate of OSA in migraine patients is not greater than the general population. Luc and colleagues [50] also did not find an increased rate of OSA in children with headaches.

Parasomnias and Narcolepsy

Parasomnias such as sleep talking and bruxism occur more frequently in children with headaches [51]. Additionally, somnambulism and sleep talking are seen in greater prevalence among migraine patients than in controls [52, 53]. Within migraine, parental reports of somnambulism are higher in children with migraine with aura than in controls or those without aura (13% vs. 3%) [54]. Indeed, Guilleminault et al. [55] have hypothesized a connection between somnambulism and migraines such that age-dependent serotonin metabolism leads to the former problem in young children and the latter in older children.

Besides somnambulism, periodic limb movements also appear to occur more often in children with headaches. A study on periodic limb movements in children [56] showed migraine patients with higher NREM parasomnias compared to control. Within the high periodic limb movement group, 26.47% had a high frequency of movements (periodic limb movements >5 per hour). The children in this group also had higher headache frequency, intensity, duration, and morbidity as well as less efficacious preventative and rescue treatments in comparison to children with migraine but without high limb movements. Restless leg syndrome has also been shown to occur four times more in children with migraines than in children without headaches [57].

The relationship between narcolepsy and headaches has not been as investigated as the parasomnia-headache relationship. Evers and DMKG Study Group [58] showed an increased prevalence of nonspecific headache in narcolepsy patients but not an increased prevalence of migraine specifically. Luc et al. [58] looked at the inverse relationship and found an increased prevalence of narcolepsy in children with headaches. A Taiwan nationwide longitudinal study showed an increased risk for the development of narcolepsy in children with migraine [59]. A proposed mechanism between narcolepsy and migraine has focused on shared orexin pathophysiology within the hypothalamus [60, 61].

Movement Disorders and Headaches

While the category of movement disorders encompasses a range of disorders from relatively benign (e.g., essential tremor) to more malignant (e.g., Huntington's disease), the most common movement disorder in childhood is a tic disorder. Thus, potential comorbidities between headaches, motor or vocal tics, and Tourette's syndrome are the most significant to consider.

Kwak et al. [62] studied 100 patients (adults and children) with Tourette's syndrome and found that 25% met the criteria for migraine, a rate four times as high as the prevalence in the general population. A more recent study [63] of exclusively young adults and pediatric Tourette's patients (age < 21) confirmed the Kwak study, revealing that migraine was four times more common and tension-type headache was five times more common than in the general pediatric population. Pathophysiologically, it has been hypothesized that a functional impairment in basal ganglia-thalamocortical circuitry may be the connecting thread through genetic, aminergic, and psychiatric mediators that have also been proposed [64].

Neuropsychological and Psychiatric Comorbidities

A plethora of research has explored the relationship between headaches and neuropsychological and psychiatric disorders. Certainly, given the morbidity of headache disorders, it is unsurprising that children with recurrent headaches experience mental and cognitive distress that may cross the threshold into true dysfunction. Machnes-Maayan et al. [65] revealed that up to 65.5% of pediatric patients with migraine have at least 1 psychiatric disorder. And the connection between these issues is not unidirectional. Indeed, a positive feedback loop exists between headaches and childhood psychopathology—headaches lead to internalizing symptoms and psychopathology, which in turn lead to somatic symptoms such as headaches [66]. Additionally, Powers et al. [67] showed that the presence of psychiatric comorbidities in children with headaches leads to a lower likelihood of treatment success. Thus, it is important for clinicians to understand the problems that may arise and how they may impact headache trajectory and treatment.

ADHD and Learning Disabilities

Since one of the biggest responsibilities a child has is to attend school and acquire knowledge, mild neurocognitive problems such as ADHD and learning disabilities can have a profound impact on a child's life and developmental trajectory. Globally, the prevalence of ADHD in children is approximately 2.2%, while the prevalence of learning disabilities is approximately 10%. However, children with headache disorders, and migraine specifically, have an elevated risk of both ADHD and learning issues [68, 69]. A study by Leviton [70] showed that 40.4% of children with recurrent headaches had academic difficulties. Said academic difficulties are often a trigger for referral to a neurologist for consultation. In fact, Strine et al. [71] found that children referred for headaches are 2.6 times more likely to have inattention or hyperactivity. These traits are often present prior to the onset of headaches. A cross-sectional study of 10,198 children between 1999 and 2004 showed that children with frequent or severe headache have twice the risk as children without headache to have a prior diagnosis of ADHD [69]. Yet, other studies have indicated that a diagnosis of headache simply increases the risk of either inattention/hyperactivity traits or clinical ADHD. A 2010 study of Brazilian school children showed an elevated relative risk for children with definitive migraine and probable migraine (2.6 and 2.1, respectively) [72]. Arruda et al. [73] looked at 8599 school children and found a significantly higher prevalence of inattention symptoms in children with migraine or tension headaches. Additionally, their study showed an increased relative risk (2.9) of ADHD in children with migraine (inclusive of episodic, chronic, and probable) and an increased risk (1.7) in children with tension headache (inclusive of episodic and probable).

In terms of learning difficulties other than ADHD, various studies have shown that, compared to children without headaches, children with recurrent headaches appear to have slower processing speed [74], deficits in short- and long-term memory performance [75], and lower scores in intelligence quotient scale and verbal comprehension score [76]. However, there are areas of child cognitive performance that do not seem to be impacted by headaches. Haverkamp et al. [77] looked at information processing in childhood migraineurs and saw no difference in sequential and simultaneous processing compared to controls.

OCD and Anxiety Disorders

Anxiety disorders are a common problem in childhood and adolescence, occurring in 15–20% of the population [78]. Several studies (e.g., ([65, 79, 80] have illustrated that anxiety disorders occur more frequently in children with headaches than in the non-headache population. Indeed, Bellini et al. [79] revealed that anxiety is the most common internalizing symptom endorsed by children with headaches. Specifically, in a clinic-based sample of 83 children aged 5–17, Machnes-Maayan et al. [65] showed that anxiety was present in 68.8% of children with tension-type headache and 56.3% of children with migraine compared to 9.1% in children without

headaches. The presence of anxiety also leads to an increased risk of both migraine and tension-type headache persistence [22].

Though nonspecific anxiety trait or generalized anxiety disorder is present in increased rates among children with headaches, specific anxiety disorder subtypes such as phobias and obsessive-compulsive disorder have also been linked to headaches ([81–83]. Vulic-Prtoric et al. [80] revealed that children with headaches have significantly more obsessive and compulsive problems than those without headache, 11.6% vs. 5.1%. In a 2013 study by Smitherman, Kolivas, and Bailey, school phobia showed the highest association with migraine followed, in order, by phobic disorder, generalized anxiety disorder, and OCD.

Mechanistically, it has been hypothesized that children with frequent headaches often experience hyperalgesia and develop fear of pain, both of which are linked with anxiety and are important factors in chronification of headache ([84, 85]; Noseda et al. 2014). A study by Masruha et al. [86] supported this thought by showing that chronic migraine in adolescents was associated with high social anxiety score while no difference seen between episodic migraine and non-migraine population. Additionally, there may be functional links between mechanisms involved in anxiety and those involved in chronic pain, e.g., serotonin dysfunction, hormones, and HPA dysfunction ([85, 87].

Childhood Trauma and PTSD

A large nidus of psychopathology in children can be linked to trauma [88]. As with anxiety, a connection exists between childhood trauma, psychiatric disorders, and migraine [89]. A plethora of studies (e.g., ([90–92] have looked at the relationship between emotional, physical, and sexual abuse, as well as bullying, and have found higher rates of these adverse childhood events in children with headaches and migraines. Juang et al. [93] studied children in a school-based population and discovered that the rate of physical abuse was significantly higher in children with chronic daily headache than in controls (10% vs. 0%, $p = 0.012$). Fuh et al. [94] also found associations between physical maltreatment and headache frequency, headache severity, and migraine specifically. In a community sample, Peterlin et al. [95] showed PTSD to be more prevalent in both episodic and chronic migraine patients than in non-headache controls. Unsurprisingly, abuse can be a factor in headache transformation. A headache clinic-based study of 1348 migraine patients showed that emotional abuse is not only associated with chronic migraine (OR 1.77) but increases the risk for transformation of episodic to chronic migraine (OR 1.89) [96]. Lastly, the path from abuse to headache is as strong as the connection between abuse and psychopathology. A meta-analysis of three studies showed a similar effect size (0.94) for the association between child abuse and headache/migraine as with the association between child abuse and psychiatric sequelae [97]. Notably, there may be an epigenetic mediator of this connection—polymorphisms of serotonin transporter gene (5-HTLLPR) are associated with vulnerability to PTSD following stressful life events [98].

Depression

Though prevalence is slightly less than that of anxiety disorders, major depressive disorder (MDD) occurs in 11–20% of children and adolescents [99, 100]. And while depression is common during childhood among the population at large, the prevalence in headache patients can be higher with various studies (e.g., ([65, 101, 102] showing a prevalence ranging from 4 to 25%. McWilliams et al. [103] showed that depression is more common in migraine than in other chronic pain disorders. This association is unsurprising given that internalizing disorders are commonly reported in children with headaches [79]. Once a child's headaches transform into chronic daily headaches, the risk for depression is even higher [104, 105].

Bidirectionality is a key component of the relationship between depression and headaches. Depression can predict headache onset ([106, 107] and migraine is associated with the development of depression ([108, 109]. In a retrospective study of 12 years of data utilizing more than 15,000 children, Modgill et al. [110] showed that children with migraine were 1.6 times as likely to develop depression compared to children without migraine. Additionally, compared to children without depression, children with depression were 1.4 times more likely to develop migraine. Blaauw et al. [111] found similar results when looking at headaches, anxiety, and depression symptoms in a population of 2399 Norwegian adolescents aged 12–16 at baseline and 4 years later. The study showed that, in children with headaches, higher baseline scores of anxiety and depression were associated with more frequent headaches—especially migraines—4 years later. In addition, in children without headaches, higher baseline scores of depression and anxiety were associated with the 4-year development of migraines.

This feedback loop, however, does not operate in a vacuum. Its influence is evident in one of the clearest effects of headache morbidity in childhood: school absenteeism. Rousseau-Salvador and colleagues [112] examined a pediatric headache clinic population of 368 children with either chronic daily or episodic headache. School absenteeism was higher among children with chronic than episodic headache. However, among children with either headache frequency, those with higher depression scores missed school significantly more. Breuner et al. [113] also showed higher missed school days among children with headaches and higher depression scores.

Lastly, given the potential risk of suicide in major depression, it is imperative to recognize that suicidality can be an independent comorbidity in chronic headache. A study by Wang et al. [114] revealed similar numbers of children at high suicidal risk in chronic daily headache as those with major depression and panic disorder. Within headaches, the relationship appears to be driven primarily by migraine with aura, as well as high headache frequency (>7 days per month) [115].

Pathophysiology

Given the extensive comorbidity between depression and migraine, it is reasonable to hypothesize a genetic or molecular connection between both disorders. A plethora of research (c.f. [116]) has focused on the role of serotonin. Serotonin levels are

lower in patients with depression [117] and are also lower interictally in migraineurs [118]. Additionally, medications to increase serotonin (SSRIs) and serotonin agonists (triptans) are mainstays of depression and migraine treatment. Genetically, polymorphisms of the serotonin transporter gene (5-HTLLPR) have been associated with migraine with aura but not without [115]. Other genes have been implicated to be associated with both depression and migraine, but no definitive associations have been proved [119, 120].

While serotonin has been prominently featured as a potential connection, other neurotransmitters have also been implicated. A recent basic science study [87] suggests that complex interactions between various neurotransmitters (e.g., dopamine, glutamate, GABA, serotonin) may influence the signals between the hypothalamus and cortex in migraine and, in so doing, connect migraine to emotional, cognitive, and behavioral factors. This builds on work outlined by Muller and Schwarz [121] on the effect of glutamate in major depression.

Treatment of Psychiatric Comorbidities

As alluded to above, treatments for mood and anxiety disorders often involve the targeting of systems (e.g., serotonin, dopamine, glutamate) also implicated in migraine. The overlap is typically within the realm of preventative headache treatments. The American Headache Society recently released guidelines [122] for pediatric migraine prevention. Unfortunately, there is only evidence for one antidepressant—amitriptyline—that could potentially be used for both migraine and mood or anxiety disorders. The key word here, however, is *potentially* as tricyclic antidepressants like amitriptyline are typically less tolerated as a primary treatment for depression or anxiety than the more abundant selective serotonin reuptake inhibitors. Sadly, the SSRIs have inadequate evidence to state that they are effective in migraine prophylaxis [123]. There is, however, grade B evidence for the selective norepinephrine reuptake inhibitor venlafaxine as a migraine preventative for episodic migraine in adults [123]. Given the aforementioned information, there remains a need for further research on treatments that may be sufficient as medication monotherapy for migraine and mood and/or anxiety disorders.

Despite the limited options for combined medication treatment of migraine and psychiatric comorbidities, evidence has been emerging over the past decade for the effectiveness of cognitive behavior therapy in pediatric migraine prevention. The CBT modality has been an established part of the twenty-first-century treatment of childhood depression and anxiety [124, 125]. Ng et al. [126] pooled 14 studies of CBT for pediatric migraine for a meta-analysis and showed odds ratios of 9.11 and 9.18 for 50% or greater headache reduction immediately post-treatment and at a 3-month follow-up, respectively. Notably, the aforementioned AHS guidelines for pediatric migraine prevention specified that only the combination of amitriptyline and CBT shows strong evidence for efficacy. Amitriptyline alone has insufficient evidence [122]. Thus, it is apparent that CBT may be a necessary adhesive force for comorbid treatment.

Conclusion

As illustrated throughout this chapter, children with headaches rarely enter the physician's office alone—they are often accompanied by other medical and psychiatric disorders that affect both the presentation and course of their cephalalgia. These comorbidities along with other social and environmental factors feedback into headaches and can create a destructive feedback loop [127]. Therefore, it is imperative that the treating physician consider the entire scope of the child's history in order to formulate an effective treatment plan as well as to remain aware of the potential barricades that may complicate said treatment in the future.

Return to Case 1
Following your exam, you discuss with your 13-year-old patient and her mother that what she is experiencing is episodic migraine based on her history. You also mention that there is concern for Tourette's syndrome given her motor and vocal tics. What is explained is that there is an overlap between migraines and other neurological concerns, such as tic disorders, and as such they can often be seen as comorbid conditions. What is also reviewed is that it is important to work out a treatment plan that can help both her migraines and her Tourette's syndrome. Fortunately, her tics are not causing physical harm/injury or any psychosocial concerns so can be treated conservatively. A multitiered approach is laid out to them, including lifestyle modifications as a foundation. Complementary and alternative therapies are reviewed as an adjunct option, with cognitive behavioral therapy recommended as this has been shown to be beneficial for migraine treatment, both as a prophylactic and as an adjunct rescue treatment, as well as for tic disorders, especially when there is a premonitory urge/sense associated with the tics. No daily prophylactic treatment was initiated, but she was encouraged to treat her migraines acutely with ibuprofen, fluids, and rizatriptan. Follow-up is set for 3 months to see how things are progressing with the option to return sooner if her headaches are worsening.

Return to Case 2
Following your exam, you discuss with your 14-year-old patient and his mother that what he is experiencing is most likely NDPH, tension-type subtype. What is explained is that, while his exam is normal and there are not any red flags in his history regarding his headaches, a general workup is recommended to include imaging and screening labs (these are obtained as an outpatient and are all normal). You also review his ADHD with them and note that his Vanderbilt scores are better than when he was first diagnosed and that his treatment seems to be still working. It is reviewed that his grade decline is more likely related to his headaches, rather than his ADHD no longer being controlled. You review a multitiered treatment approach highlighting the importance of starting this as soon as possible to try to break him out of his daily pattern but also review the goals of treatment with the first step to get him back to normal functioning, including school. It is decided that a daily prophylactic will be initiated but with taking into consideration his ADHD. Several options are reviewed with gabapentin selected due to low side effect profile with titration every

2 weeks until target dose is reached. He is asked to follow up in 6 weeks to see how the treatments are helping and to review how his schoolwork is progressing.

Return to Case 3
Following your exam, you administer a depression and anxiety screen. She screens negative for depression but positive for anxiety. You review these findings with the patient and mom and note that this is a very common finding you are seeing as the pandemic has drawn on, especially for those who are used to a routine and who are struggling with the changes that were forced on them abruptly. Additionally, you review that mood and psychiatric concerns, including anxiety, are common comorbidities seen in migraine patients. You also discuss with them that her migraines have progressed from episodic to chronic and are now in need of prophylactic interventions. What is also reviewed is that it is important to work out a treatment plan that can help both her chronic migraines and her anxiety. A multitiered approach is laid out to them starting with lifestyle modifications. Complementary and alternative therapies are reviewed as an adjunct option, with cognitive behavioral therapy recommended for both her migraines and anxiety. Daily prophylactic treatment was also discussed, and it was recommended she initiate an antidepressant or antianxiety treatment as this can help both her chronic migraine and her comorbid anxiety. The possibility for a pediatric psychiatry referral was also reviewed, as this may be necessary depending on how she responds to counseling and medication management. Follow-up is set for 3 months to see how things are progressing with the option to return sooner if her headaches are worsening.

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Chapter 8
Dysautonomia and Atopy in Pediatric Headache Patients

Daniel Feldman and Ryan P. Williams

Case 1

A 14-year-old female presents to her pediatrician for her yearly physical. She has always been healthy and active, but at this visit, she describes a variety of new concerns. Since starting high school 6 months ago, the patient has been experiencing episodes of abdominal pain. In addition, though she was previously a star soccer player, she lately has been too fatigued to play her games and on some days is so tired that she cannot get out of bed. On the rare day that she is able to play, she frequently becomes dizzy, weak, and lightheaded. She has had severe throbbing headaches several days per week, mostly on the right side, which have been accompanied by light sensitivity and nausea. Her parents initially attributed the symptoms to a combination of the start of menses as well as difficulty adjusting to high school. However, what made them more concerned was an episode several days earlier where the patient stood up from a chair after finishing dinner and fainted. The patient had never lost consciousness before, and since that episode she has been standing up very slowly and noticing that she feels her heart racing. These symptoms are causing the patient significant anxiety, and her grades have declined in the last few marking periods.

On evaluation, the patient appears slightly withdrawn but does participate in the interview. Her vital signs reveal normal temperature, blood pressure 108/67, heart rate 80, and respiratory rate 14. Her physical examination, including neurologic

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exam, is completely normal. The patient is asked to stand and feels quite dizzy and develops slightly blurred vision. Her blood pressure when standing is 110/68 and heart rate is 130.

Dysautonomia

Dysautonomia is a general term referring to a dysfunction of the autonomic nervous system, which controls involuntary bodily functions. It is an increasingly recognized and often debilitating condition, affecting approximately two million people in the United States [1]. In the pediatric and adolescent population, dysautonomia often begins with orthostatic intolerance, which may involve recurrent bouts of syncope and/or postural lightheadedness. Quite often, this cardinal symptom is followed by a headache, which is then succeeded by multiple systemic complaints. The most prevalent form of orthostatic intolerance is postural orthostatic tachycardia syndrome (POTS). First discovered by Low and Colleagues at the Mayo Clinic in 1993, POTS affects an estimated 500,000 people in the United States [2]. Most patients are females between the ages of 12 and 25. Despite this, it is a condition in which the diagnosis is frequently delayed, which prevents the patient from being managed appropriately. In addition, migraines and POTS frequently present as comorbid conditions in the pediatric population. This relationship is frequently missed, often because the autonomic symptoms are felt to be a by-product of the migraine pathophysiologic process. However, at least 25% of POTS patients have migraines at the time of diagnosis [3].

In this section, we will provide a brief overview of the autonomic nervous system anatomy, embryology, and physiology. We will then describe the epidemiology, clinical presentation, and management strategies of POTS, and more specifically of the comorbid headaches that are frequently seen in this disorder. We will also review some other dysautonomias that may be seen in the pediatric population in which headaches are a common feature. We will conclude this section with a general summary of the approach to a pediatric headache patient with concurrent dysautonomic symptoms.

Autonomic Nervous System

The ANS is a visceral, largely involuntary motor/effector system, which is divided into sympathetic and parasympathetic divisions. Each division has a central and peripheral component. The ANS has an enteric division as well. Outflow is regulated in part by the central autonomic network (CAN), which maintains relationships with visceral sensory neurons via afferent input from the vagus nerve and relays transmission through the nucleus tractus solitarius to the hypothalamus, amygdala, and forebrain [4]. Embryologically, the ANS originates from neural crest cells, which migrate and evolve into autonomic ganglia. There are various growth

Table 8.1 Organ-based autonomic nervous system functions [4]

Organ	Sympathetic nervous system	Parasympathetic nervous system
Eye-pupil	Dilation	Constriction
Eye-ciliary muscle	Relax (far vision)	Constrict (near vision)
Lacrimal gland	Slight secretion	Secretion
Salivary glands	Slight secretion	Secretion
Heart	Increased rate	Decreased rate
Lungs	Bronchodilation	Bronchoconstriction
GI	Decreased motility	Increased motility
Kidney	Decreased output	None
Bladder-detrusor	Relax	Contract
Bladder-sphincter	Contract	Relax
Blood vessels	Constriction	Dilation
Penis	Ejaculation	Erection

factors which promote this evolution. For example, *MASH1* and *PHOX 2B* genes are transcription factors needed to promote the differentiation of neural crest cells to the developing ANS, and nerve growth factor (NGF) promotes migration and maturation.

Among other functions, the peripheral autonomic nervous system assists in maintaining homeostasis and responding to stress. It does this using multiple neurotransmitter systems. For both the sympathetic and parasympathetic systems, preganglionic innervation is largely cholinergic. For the sympathetic nervous system, the main postganglionic neurotransmitter is norepinephrine, though other transmitters such as substance P, dopamine, and vasoactive intestinal peptide (VIP) are also important [4]. The sympathetic and parasympathetic nervous systems are often, but not always, antagonistic in function. Some of the major functions of the ANS are summarized in Table 8.1.

POTS Introduction

POTS is one of the most common presentations of syncope and presyncope secondary to autonomic dysfunction [5]. It is more common in women than men with a ratio of approximately 5:1. It is a heterogeneous clinical syndrome that, in the broadest sense, is characterized by sustained and excessive sinus tachycardia upon standing in the absence of orthostatic hypotension and with chronic symptoms of orthostatic intolerance. It is estimated to affect between 0.1 and 1% of the US population. Despite the relatively high prevalence, it remains a poorly understood condition. As a result, there are often delays in diagnosis or the condition may be misdiagnosed entirely. Indeed, data from a survey of 700 POTS patients revealed a median time to diagnosis of just under 6 years, with 27% of respondents reporting having been seen by more than 10 physicians between symptom onset and diagnosis

[6]. Additionally, 83% of patients in the same survey reported being given a psychiatric diagnosis prior to being diagnosed with POTS. The diagnostic evaluation of POTS, therefore, requires a meticulous and individualized approach that is centered on not only documenting excessive postural tachycardia, but also excluding other conditions that mimic autonomic dysfunction or are causative of it.

Of note, this discussion will focus on primary POTS, the more common, idiopathic form of the disease. However, it should be recognized that there also exists secondary POTS, wherein POTS symptoms occur in conjunction with a known disease or disorder [7]. These include diabetes, systemic lupus erythematosus (SLE), and paraneoplastic syndrome in the setting of various cancer types. In the latter case, POTS is thought to develop in response to the production of autoantibodies against acetylcholine receptors in the autonomic ganglia.

Pathophysiology

Upon standing, there is an immediate shift of 500–1000 mL of blood to the capacitance vessels in the lower extremities and splanchnic circulation [5]. In addition, there is a secondary shift wherein 10–25% of plasma volume is driven out of the vasculature and into the interstitial space in response to gravitational stress. As a result, there is impaired venous return to the heart, which in turn leads to decreased blood pressure. The autonomic nervous system compensates for these changes by stimulating sympathetic and suppressing parasympathetic nerve activity via baroreceptors in the carotid sinus and aortic arch. This results in increased systemic vascular resistance and enhanced venous return to the heart. Any impairment in these compensatory mechanisms can result in orthostatic symptoms. However, it should be noted that this is a rather oversimplified explanation. Indeed, POTS is a pathophysiologically heterogeneous disorder, as there have been attempts to classify it into a hyperadrenergic form (with elevated norepinephrine levels), a neuropathic form (with patchy denervation of sympathetic fibers in the lower extremities), and the forms associated with deficiency in norepinephrine transport or antibodies directed against the ganglionic acetylcholine receptor [8].

Clinical Presentation

One of the main reasons for the lack of understanding of POTS is the incredibly broad range of symptoms with which patients present, as well as the timing. Symptoms of POTS may develop acutely (<1 month), subacutely (1–3 months), or more insidiously (>3 months) [9]. An antecedent history of infection is reported in upwards of 50% of patients. Symptoms of orthostatic intolerance are common and include lightheadedness, palpitations, and near syncope. Notably, however, any symptoms that present when the patient is upright and resolve or improve with

Table 8.2 Common POTS symptoms [10]

Symptoms	No. (%) of patients (N = 152)
Orthostatic	
Light-headedness or dilzziness	118 (77.6)
Presyncope	92 (60.5)
Weakness	76 (50.0)
Palppitations	114 (75.0)
Tremulousness	57 (37.5)
Shortness of breath	42 (27.6)
Chest pain	37 (27.6)
Loss of sweating	8 (5.3)
Hyperhidrosis	14 (9.2)
Exacerbation by heat	81 (53.3)
Exacerbation by exercise	81 (53.3)
Exacerbation by meals	36 (23.7)
Exacerbation associated with menses	22 (14.5)
Nonorthostalic	
Bloating	36 (23.7)
Nausea	59 (38.8)
Vomiting	13 (8.6)
Abdominal pain	23 (15.1)
Constipation	23 (15.1)
Diairrhea	27 (17.8)
Bladder dysfunction	14 (9.2)
Pupillary dysfunction	5 (3.3)
Generalized associated	
Fatigue	73 (48.0)
Sleep disturbance	48 (31.6)
Migraine headache	42 (27.6)
Myofascial pain	24 (15.8)
Neuropathic pain	3 (2.0)

recumbence may reflect orthostatic intolerance and may be symptoms of POTS. These include nausea, chest pain, paresthesia, vertigo, dyspnea, neck pain, flushing, and headache. Moreover, posture is not the only trigger of symptoms, as some patients report feeling worst in the mornings, while others note exacerbations with heat, showering, food ingestion, menses, or physical exertion, among other provocative factors. Fatigue is a prominent symptom in many patients and is one of the most debilitating. Other non-orthostatic issues include cognitive complaints (frequently described by patients as “brain fog”), urinary dysfunction, and thermoregulatory or sweating impairment. Table 8.2 provides an overview of some of the symptoms of POTS and their prevalence based on a study published in 2007 by Theiben and colleagues [10]. As we know now and as will be discussed later, migraine prevalence in POTS is likely considerably higher than what was reported in this study.

As with all conditions, a thorough medical history is critical in the evaluation of POTS. This should include an assessment of symptom onset and progression, as well as a thorough review of any possible conditions that may have preceded the

development of POTS. Importantly, however, a substantial number of POTS patients will have no identifiable antecedent event or precipitant for their condition [11]. Family history is important, though more so to rule out any significant cardiac history, as a family history of orthostatic intolerance is reported only by a minority of patients. Fluid and caffeine intake, level of physical activity, sleep pattern, and medications and/or treatments previously tried are all essential to know. Sleep disorders are highly prevalent in the POTS population, as nearly all patients report unrefreshing sleep, among many other conditions [12].

The general physical examination of a suspected POTS patient should include a careful cardiac, dermatologic, and neurological evaluation. Supine and standing heart rate and blood pressure measurements should be taken. A thorough cardiac examination is necessary to exclude structural heart disease. Neurological examination may reveal pupillary dysfunction, or a small fiber neuropathy, providing further evidence of autonomic dysfunction. Dermatologic exam should check for excessive resting sweat on the palms and feet, which may suggest excess sympathetic activation, while dry skin may indicate secretomotor impairment [9]. Skin discoloration may be a sign of vasomotor instability. Skin and joints should also be checked for hypermobile Ehlers-Danlos syndrome (EDS), a condition frequently comorbid with POTS.

Diagnosis

The majority of the diagnostic evaluation of POTS is predicated on ruling out conditions that may mimic or exacerbate the condition, as well as identifying other comorbid conditions. Basic laboratory testing that should at least be considered in all patients includes a complete blood count, thyroid function studies, AM cortisol, plasma and urinary metanephrines, vitamin B12, and possibly celiac testing, antinuclear antibody, and Sjogren antibody testing [13]. In patients with significant systemic symptoms, additional antibody testing to evaluate for autoimmune etiology should be considered. This may include voltage-gated potassium and calcium channel antibodies, and ganglionic acetylcholine receptor antibodies.

Cardiac testing should strongly be considered in all patients and can include some combination of electrocardiogram, echocardiogram, and 24-h Holter monitoring. These are necessary to rule out underlying arrhythmia or structural heart disease. Neurologic testing may include a brain MRI if the POTS patient presents with a new daily headache or a headache accompanied by systemic symptoms (further discussed later in this chapter). A headache with a significant postural component should prompt an investigation of spontaneous intracranial hypotension in the setting of a CSF leak, and on history alone, this can be difficult to delineate in a POTS patient whose headaches frequently do worsen with standing. A brain MRI with and without contrast may be useful in this regard as well, as in the case of intracranial hypotension, it may show engorged venous structures of pachymeningeal enhancement, among other findings. Neuropathy in POTS patients is primarily small fiber,

so nerve conduction studies are often unrevealing. In these patients, a skin biopsy could be considered [9].

Autonomic testing should be considered in all cases of suspected POTS to both confirm the diagnosis and possibly allow for characterization into a specific pathophysiological subtype [13]. Tilt-table testing is the mainstay of autonomic evaluation and should be done at 60° for at least 10 min. A sustained heart rate increment of 30 or more beats per minute or a heart rate above 120 beats per minute in the absence of orthostatic hypotension is suggestive of POTS in the appropriate clinical context. In the pediatric population, however, a sustained increase of 40 or more beats per minute is frequently used to aid in the diagnosis. In many cases, this can be noted in the clinical setting via a 10-min standing test where the patient lies flat for 5 min and had a resting heart rate and blood pressure taken. The patient then stands upright for 10 min with heart rate and blood pressure taken several times over the 10 min. POTS can be diagnosed if there is sustained elevation of more than 40 beats per minute above resting heart rate without hypotension in a pediatric patient and that patient is symptomatic during the test. Symptoms may include, but are not limited to, vision changes, dizziness/vertigo/lightheadedness, diaphoresis, skin changes, dependent edema, headache, and nausea. Sudomotor function is also frequently checked, particularly in patients with hypohidrosis or hyperhidrosis. This is most often done via quantitative sudomotor axon reflex testing (QSART) and, less commonly, thermoregulatory sweat testing (TST). QSART provides an assessment of postganglionic sympathetic sudomotor function.

Gastrointestinal, genitourinary, and sleep evaluation should also be considered in POTS patients as indicated by their symptoms. GI evaluation may include imaging or gastric emptying studies. GI evaluation may include urodynamic testing. Polysomnography may be of significant utility in patients with fatigue, daytime sleepiness, or sleep disturbances.

Lastly, as with most medical conditions, it is important to consider whether orthostatic intolerance may be induced by a medication. Diuretics, anxiolytics, and vasodilators all impair venous return to the heart and may cause similar symptoms to POTS. A thorough review of the patient's medication list is essential in the POTS workup.

POTS and Headaches

Headache prevalence in the pediatric population is likely underestimated given that many patients do not seek medical care. Migraine prevalence increases throughout childhood, from 5% in elementary school children up to 30% of high school-aged children [14]. There is a significant overlap between these conditions, which may be a by-product of the pathophysiology. Notably, like POTS, pediatric migraine is three times more common in girls as compared to boys [14]. The trigeminal nucleus, central to the underlying migraine process, has neurotransmitters with vasodilatory properties such as calcitonin gene-related peptide (CGRP) and substance P. These

neurotransmitters, when studied in vivo, have been found to promote facial flushing and a slight increase in temperature when trigeminal branches are stimulated [15]. Similar vasodilation changes are seen in POTS as described above, particularly in neuropathic POTS where there is sympathetic denervation in the lower extremities.

Patients with POTS experience both orthostatic and non-orthostatic headaches. A study of 24 POTS patients aimed to further explore the headache spectrum in these individuals [16]. Patients underwent a battery of autonomic tests, and symptoms were assessed. Of these patients, 58% reported orthostatic headache during daily activities. Following head-up tilt (HUT) testing, 62.5% of patients reported the development of a headache. Younger age and increased duration of upright posture were predictive of increased incidence of orthostatic headache. On the other hand, non-orthostatic headache, particularly migraine without aura, occurred in almost all patients (95.8%). Though the sample size was small, this study further illustrates the comorbid nature of migraine and POTS, as well as the high prevalence of headaches in the POTS population. It should also be noted that orthostatic intolerance in adolescents frequently appears after an identifiable trigger such as viral illness or injury, which is similar to the onset of a headache in a new daily persistent headache (NDPH) syndrome. The main secondary headaches that are of particular concern in the POTS population include pain from insufficient orthostatic blood flow to head and neck structures as well as pain related to spontaneous intracranial hypotension. The former is usually responsive to volume expansion, while the latter can sometimes be managed conservatively with bedrest and caffeine but may require an epidural blood patch [17].

Management

The treatment of both POTS and migraine should involve a multisystem approach. Fortunately, given the pathophysiologic overlap between the two conditions, there are some treatments that are effective for both disorders. Comprehensive treatment frequently involves a multidisciplinary team that may consist of neurologists, psychiatrists, physiatrists, cardiologists, dermatologists, and physical therapists, among others. It is important to delineate whether a patient actually has POTS or whether they have dysautonomia secondary to migraine, as some medications may be more optimal if a patient has both conditions.

The multitiered approach to managing dysautonomia and POTS begins with lifestyle modifications [15]. The patient should be appropriately counseled about the condition(s) and to try avoiding conditions that provoke symptoms. Patients should be advised to take shorter showers and baths and avoid excessively warm water temperature, saunas, and prolonged sun exposure [8]. Sleep hygiene is important, as is adequate hydration. In patients with normal autonomic responses, the recommendation has been to drink at least 1.5–2 L of fluid daily. For patients with POTS or another form of orthostatic intolerance, the fluid intake should be at least 2–3 L. Salt intake is also vital for increasing intravascular volume. Recommendations vary, but

a daily dose up to as much as 10–12 g has been suggested [18]. More often, 2–4 g of salt is suggested to start, but this can be increased based on symptoms and response. Aerobic exercise is also quite helpful, as physical activity increases venous return. Postural counter maneuvers that use skeletal muscles as a pump in order to improve venous return have also been shown to be efficacious [18, 19]. These include standing with one's legs crossed, squatting, fidgeting, standing with one leg on a chair, or sitting in the knee-chest position. A supportive elastic hose can be used to increase peripheral vascular resistance and decrease venous pooling in a mechanism similar to that of exercise. These lifestyle modifications are essential as without them pharmacotherapy will be of limited utility.

Complementary therapies comprise the next tier of treatment. These include physical therapy, cognitive behavioral therapy (CBT), biofeedback, and massage/relaxation therapy [17]. There is evidence for the use of vitamins in migraine prophylaxis, specifically riboflavin (B20, magnesium, and coenzyme Q10), and for vitamin B12 and vitamin C in POTS [11, 17, 20]. Melatonin is used in both migraine and POTS due to its ability to improve sleep and also for its anti-inflammatory properties.

The final tier of management is pharmacotherapy. Various classes of medications are used in the management of both POTS and migraine, particularly given the pathophysiologic overlap described earlier in this chapter. However, it is also important to note that some medications that are commonly used in migraine prevention may actually worsen POTS symptoms. For instance, tricyclic antidepressants (TCAs), which are commonly used effectively for migraine prophylaxis, may worsen the dry mouth, constipation, and fatigue that are often seen in POTS patients [17]. Venlafaxine, an SNRI, has level B evidence for its effectiveness in migraine prevention, but may in some cases worsen symptoms of tachycardia or palpitations. Topiramate, which has level A evidence for migraine prevention, has numerous well-described adverse effects, but perhaps the most notable is cognitive slowing, which may be quite bothersome for POTS patients who describe "brain fog."

Beta-blockers, such as metoprolol and propranolol, primarily blunt heart rate acceleration and also allow more time for left ventricular filling [8]. Most patients with POTS who are initially treated with beta-blockers have some improvement, and lower doses seem to be more effective than higher doses [21]. Unfortunately, many patients with POTS are unable to tolerate the higher doses that are typically used in migraine prophylaxis.

Volume expanders such as fludrocortisone and vasoconstrictors like midodrine are frequently used in the treatment of POTS and orthostatic hypotension. Data is lacking, however, on their efficacy in migraines and other headache types. Cyproheptadine, though only of level C evidence in terms of its effectiveness for migraine prevention in adults, can be particularly helpful in augmenting appetite in POTS patients with anorexia. CGRP antagonists are the newest class of medications used in migraine prophylaxis, but data is extremely limited on their use in POTS patients. Similarly, onabotulinum toxin A (Botox) has also been shown to be effective for the treatment of chronic migraine, but has not been studied specifically in migraine.

Atopy and Headaches

Atopic illnesses such as asthma, eczema, and allergic rhinitis are common childhood disorders. Allergic rhinitis, in fact, is the most common chronic disease in children. Given the prevalence of atopy in childhood, it is unsurprising that children with primary headache disorders are also often affected with an atopic disorder. Yet, the rate of co-occurrence is higher than predicted by chance. In an epidemiological study in children with migraine, Sillanpaa and Aro [22] revealed that 39.5% of boys and 46.2% of girls had allergy symptoms. Specific atopic disorders (e.g., asthma) have been seen in 20% of migraine patients, with rates higher in girls (15.8%) than boys (7.1%) [23] [24]. A 2014 study by Ozge and colleagues in children under 18 looked at 438 patients with migraine and 357 patients with tension-type headaches. Within the data, the association between migraine and atopy peaked between ages 11 and 14. They found a significantly higher rate of migraine patients with atopy than tension-type patients. Additionally, migraine-with-aura patients were noted to have significantly more atopic disorders than those without aura [25]. A more recent database study of Israeli children [26] showed a migraine prevalence of 3.8% in children with asthma compared to 1.8% in children without asthma.

Besides the increased prevalence of allergy disorders in migraine patients and vice versa, severity and morbidity have been seen to be correlated. Martin et al. [27] performed allergy testing on 536 allergic rhinitis patients with migraine looking at the level of allergen reactivity. They found that low levels of reactivity ($\leq$45% of 20 allergens) were correlated with less severe and less morbid migraines in patients less than 45 years of age. Munoz-Jareno et al. [28] performed a case-control retrospective study of 5–15-year-old children and showed that not only was the prevalence of dermatitis, rhinoconjunctivitis, and asthma higher in migraine than in controls but the problems were also more severe.

Pathophysiology

It is well known that an inflammatory cascade leading to vascular dilatation and leakage is part of the pathophysiology of migraine. Thus, immune system dysfunction is theorized to be a bridge connecting migraine and atopic disorders. Indeed, asthma has occasionally been referred to as a "pulmonary migraine" [29]. Ozge et al. [30] observed that patients with migraine had lower pulmonary capacity on pulmonary function tests both ictally and interictally. Though direct mechanistic connections have not yet been proven, steps implicated in both migraine and atopy such as platelet aggregation through platelet-activating factor and substance P secretion from C fibers present in both the trigeminovascular system and the airway indicate a common pathway [31]. Within migraine patients, higher levels of eosinophils and IgE are correlated with a history of atopy [30]. Additionally, compared to patients with tension-type headaches and healthy controls, migraine patients have a

higher ratio of IL-1β, IL-2, and IL-6 to TNF-α [32]. Bellamy et al. [33] looked at the levels of vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) in patients with rhinosinusitis, migraines, and controls and found that the levels of both peptides were higher both during and between attacks in the sinusitis and migraine groups. CGRP levels were also higher at baseline in the migraine group compared to both the rhinosinusitis and control groups.

Management

Given the potential ontological connections between migraine and atopy, it is unsurprising that treatments of bothersome symptoms may be similar. Allergies often lead to symptoms such as lacrimation, rhinorrhea, and nasal congestion that are best categorized as cranial autonomic symptoms. While there are specific headache disorders—trigeminal autonomic cephalalgias—of which these cranial autonomic symptoms are the cardinal feature, these headaches are rare in children. These autonomic symptoms, however, are often present in migraines and, indeed, have been shown to be an independent diagnostic feature of childhood migraine [34, 35]. Martin et al. [27] noted improvement in migraine among comorbid allergy patients who were treated with immunotherapy. Antihistamines such as cyproheptadine, N-alpha-methyl histamine injections, and montelukast have been studied as possible migraine prevention medications. Unfortunately, only the antihistamine injections have level B evidence for prevention. Cyproheptadine has level C evidence [36]. Brandes et al. [37] performed a randomized double-blind placebo-controlled trial on montelukast for migraine prevention in adults and showed no difference between placebo and drug; thus, montelukast is thought to be ineffective for prophylaxis of migraine. Lastly, immunomodulatory CGRP medications were first introduced to the commercial market in 2018 and have shown respectable results in the prevention of migraine.

Conclusion

The main key is recognizing and diagnosing the entire patient, including possible comorbidities, so that appropriate treatment can be initiated. When thinking about comorbidities, POTS should be considered in any young patient, particularly females, presenting with symptoms affecting multiple body symptoms, especially when the symptoms worsen in the upright position. Evaluation of POTS patients should include a careful history as well as thorough neurologic, cardiac, and dermatologic examinations, and when necessary, ancillary testing such as a tilt-table testing is the mainstay of autonomic evaluation in POTS. Conversely, a sustained heart rate increment of 40 or more beats per minute in the pediatric population or a heart rate above 120 beats per minute is suggestive of POTS and can be identified via a

10-min standing test. Of note, similarly to pediatric headache, the management of POTS involves a multitiered strategy including lifestyle modifications, complementary therapy, and pharmacotherapy. Atopy is also commonly found in pediatric headache patients. Similarly to dysautonomia, there is overlapping pathophysiology to potentially explain this overlap. Based on this, when atopy and headaches are seen in the pediatric population, there are certain pharmacologic interventions that may be considered.

Return to Case 1

After her exam, you discuss with the patient and her mother about your suspicions that she likely has POTS as well as migraines. You review that these are common conditions often seen together and that it is not unusual for them to present around this age, shortly after puberty. As a precaution, you recommend a few screening labs including a complete blood count, comprehensive metabolic panel, and thyroid screen as well as some viral studies including a monospot. All of her tests come back negative or normal. She also gets an electrocardiogram, which is also normal. A tilt-table test is discussed, but given her exam and history, it is decided to treat her first but pursue further evaluation if she does not respond to the recommended treatments. A multitiered approach to management, as described above, is reviewed with the aim to improve her current quality of life. Lifestyle modifications are reviewed to include better sleep, a marked increase in her fluid, namely water, intake, increased salt intake as well as smaller but more frequent meals and snacks, and slow return as tolerated to activity and exercise. She is referred to physical therapy as well as cognitive behavioral therapy for both POTS and migraine management. Additionally, medications such as a beta-blocker, which can help both POTS and migraines, are reviewed, but it has been decided to pursue these next after conservative measures have been given a chance. She is asked to return for a checkup in 4–6 weeks.

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Part IV
Treatment of Pediatric Headache: A Multi-tiered Approach

Chapter 9
Lifestyle Modifications, Complementary/ Alternative Therapies, and Nutraceuticals

Lindsay Cirincione

Case 1

Alice is a 16-year-old Caucasian female who presented to our multidisciplinary clinic after experiencing headache once or twice weekly for approximately 6 months. Headaches were primarily bilateral and retro-orbital in location, with sharp, stabbing, and throbbing sensation. Onset of headache symptoms typically occurred in the morning, lasted all day, and averaged a 4/10 on a 0–10 pain scale. Headaches were associated with photophobia and occasionally with phonophobia and/or nausea. Presence of aura was denied. If taken early, an over-the-counter combination of acetaminophen, aspirin, and caffeine was helpful in aborting headaches, although a second dose was often needed. At the time of her evaluation in our clinic, Alice had not tried any complementary or alternative therapies. She was previously prescribed Topamax by her PCP, but this was quickly discontinued due to side effects. No other workup, imaging, or treatment had been offered. Relevant family history was significant for maternal migraine.

Alice had significant difficulty with sleep due to a demanding academic course load. At the time of her clinic visit, Alice was in the tenth grade and was taking advanced and college courses, which she identified as a significant stressor. She described feeling exhausted at the end of each school day, which leads to daily naps of 1–2 h in length. Alice spent 5–7 h completing homework each evening. During the week, she typically slept from 2:00 a.m. to 6:00 a.m., with significant difficulty falling asleep.

From a nutrition standpoint, Alice typically skipped breakfast, ate lunch and dinner, and avoided caffeine. She denied nicotine or alcohol use. Hydration was poor,

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as she drank only enough water to urinate twice daily. Alice denied getting regular exercise. From a mood standpoint, Alice endorsed significant anxiety related to school performance as well as related to the well-being of an extended family member with a chronic health condition.

Introduction

The management of pediatric headache necessitates an examination of factors, which extend beyond physical symptoms and medical history. In this chapter, we investigate what are commonly known as headache "lifestyle factors" including sleep, hydration, nutrition, and exercise. These factors are commonly known to have a significant impact on the presence, frequency, and intensity of symptoms across the spectrum of pediatric headache. Additionally, this chapter introduces several complementary/alternative therapies (CATs) and the evidence base for these less commonly prescribed but helpful adjunctive treatments. Finally, we explore what is known about commonly utilized nutraceuticals along with their respective risks and benefits.

Lifestyle Factors

The extent to which lifestyle factors impact headache presentation cannot be overstated. Without a close look at lifestyle factors in pediatric headache, successful treatment will be nearly impossible [1]. In fact, the Childhood and Adolescent Migraine Prevention program identified lifestyle factors as one of the three core treatment components; the others included NSAIDs/triptans and preventative treatment, which resulted in improvement of 60% of pediatric migraine patients [2]. A vast body of research has associated poor sleep, low levels of physical activity, skipping meals (breakfast in particular), smoking, and caffeine overuse with headache in children and adolescents [3, 4]. Despite the importance of assessing and modifying headache lifestyle factors, some research has demonstrated that fewer than 15% of children receive advice about adjusting lifestyle factors to promote headache improvement [5]. As our understanding of the significance of lifestyle factors in regard to headache deepens, it is crucial that providers address factors such as sleep, hydration, and nutrition as core components of treatment in pediatric headache.

Sleep

Sleep has been identified as a significant contributor to headache in pediatric patients. The Consensus Statement on Pediatric Sleep [6] identified specific age-based guidelines for appropriate sleep duration (Table 9.1). Young people today face

Table 9.1 Consensus statement on pediatric sleep recommendations [6]

Age	Number of hours recommended
Infants 4 months–12 months	12–16
Children 1–2 years	11–14
Children 3–5 years	10–13
Children 6–12 years	9–12
Adolescents 13–18 years	8–10

an incredible number of demands on their time, and it is easy to imagine how difficult it may be for children and adolescents involved in extracurricular activities, hobbies, and scholarly pursuits to adhere to these guidelines. Nonetheless, it is incumbent upon pediatric providers to support their patients and families in understanding the importance of adequate sleep as it relates to headache.

The complex relationship between sleep and headache is not well understood. Nonetheless, research has demonstrated that it is likely a reciprocal relationship, with sleep being associated with headache and headache itself causing sleep disturbances [7]. Insufficient sleep, problems with latency to sleep onset (time to fall asleep), low sleep duration, poor sleep quality, night wakings, nighttime restlessness, daytime fatigue, bedtime resistance, anxiety related to sleep, daytime napping, parasomnias, and disordered breathing are more common among children and adolescents with headache [7–11]. Given that sleep is likely to play an important role in the successful treatment of pediatric headache, sleep habits, concerns, and parasomnias should be considered an important part of the evaluation and treatment plan.

When evaluating sleep in children and adolescents, it is important to get a good sleep history. Self-report of sleep is notoriously unreliable. Thus, it may be helpful to have patients keep a sleep diary as well as to incorporate parents/caregivers in the collection of sleep-related information. Practitioner inquiry should run the gamut of sleep hygiene behaviors (Table 9.2) and should include information from both children and parents. In the case of adolescents, it may be helpful to interview the child and parent separately, as the child may be reluctant to disclose information in front of parents.

Once the practitioner has established a good understanding of sleep patterns, a comprehensive plan for improving sleep hygiene can be implemented (Table 9.3). Addressing sleep can result in an improvement in headache, with or without pharmacological treatment. In fact, research has demonstrated that adolescents who incorporated good sleep hygiene had a decrease in frequency and duration of migraine [11]. Sleep hygiene is an important area of intervention; however, it is often difficult for children and families to implement. It may be helpful for practitioners to support families in establishing a plan to gradually incorporate elements of sleep hygiene to reduce perceived burden of the intervention. Examples of a gradual change could include moving bedtime earlier by 15 min every few days until appropriate sleep duration is reached or gradually shortening naps until they are eliminated.

Table 9.2 Sleep factors to evaluate

• Bedtime	• Latency to sleep onset
• Bedtime routine/behaviors	• Night wakings and return to sleep
• Sleep duration	• Sleeping arrangements
• Use of electronics prior to bed	• Temperature of room/noise level
• Activities performed in bed prior to sleep	• Nightmares/parasomnias
• Daytime naps (frequency/duration/time)	• Disordered breathing
• Consistency of sleep schedule	

Table 9.3 Elements of sleep hygiene

• Consistent bedtime and routine	• Eliminate/shorten daytime naps
• Age-appropriate sleep duration	• Limit fluids 2 h before bed
• Use bed only for sleep	• Limit electronics 1 h before bed

Exercise

Physical activity should be evaluated in all headache patients, as moderate exercise has been associated with positive changes in headache presentation. Exercise may be a favorable treatment element for patients who do not benefit from pharmacological intervention or prefer not to take medications. The general recommendation for exercise in headache patients is 30–40 min of moderate activity three times per week [12]. It is important to assess symptomology and whether or not symptoms are exacerbated by physical activity. However, even if patients report an exacerbation of headache symptoms with exercise, practitioners are in a unique position to help patients pace and gradually increase their exercise with the ultimate goal of meeting the recommended weekly amount.

In a small pilot study of adult migraine patients, Darabaneau et al. [13] introduced an 8-week exercise regimen which focused on aerobic activity of 30 min three times per week. Results of this investigation indicated that when exercise reached an appropriate level of intensity, it resulted in a significant improvement in the number of migraine days per month, as well as a reduction in symptom intensity and duration. A fortunate by-product of the treatment was a significant reduction in stress. Other larger scale studies have produced similar results [12, 14–16]. While much of this research has been conducted in the adult headache population, it stands to reason that physical activity can present a number of benefits to the pediatric population, even insofar as the trickle-down effect of stress reduction, support of healthy weight, behavioral activation, and mood management, all of which can improve the cycle of pain and disability.

Hydration

The link between inadequate hydration and headache is age-old; however, surprisingly little research has been conducted in the domain of hydration in pediatric headache patients. Given the numerous benefits of adequate hydration to the

biology of human beings, it stands to reason that at baseline, headache patients would benefit from at least adequate (if not improved) hydration. Kenney et al. [16] took a broad-scale look at overall hydration in children and adolescents. Of the more than 4000 children included in the study, rates of dehydration were shockingly high, at 54.5%. Migraine patients in particular may be more sensitive to dehydration, which is a common trigger for migraine onset [17]. When hydration is addressed and supplemented in headache patients, duration and intensity of headache symptoms decrease and quality of life improves [18, 19]. While more well-controlled studies are needed in the pediatric population, addressing hydration in children is a cost-effective and low-risk intervention which carries benefits across a number of symptom domains. Anecdotally, we have found that in our clinic, children and adolescents often have difficulty accurately reporting the amount of water they drink in a given day. When this is the case, it can be helpful to assess the frequency and color of urination in order to establish a baseline. Additionally, many schools require medical rationale for children to carry a water bottle throughout their school day. Thus, it is important that providers investigate access to adequate hydration in the school setting and provide documentation as needed.

Healthy Weight

Exercise is important not only for the direct effects it has on the mitigation of headache symptoms, but also for the maintenance of healthy weight. There is a strong link between body mass index (BMI) and migraine prevalence, frequency, and headache-related disability [20, 21]. Obesity in childhood can quadruple the risk of migraine and is associated with more symptoms such as nausea and missed school days than in peers of healthy weight [21]. Thus, it is extremely important that practitioners consider weight as not only a factor that may predispose children to migraine, but also one that can increase symptom severity and disability. In children, BMI should be monitored and addressed as a component of headache treatment.

Nutrition

Diet in the pediatric headache population is a controversial topic. Many families, in an attempt to provide relief for their children's headache symptoms, are quick to adopt an elimination, gluten-free, dairy-free, ketogenic, or other restrictive diet. Nonetheless, the American Headache Society recommends that headache patients avoid restricting entire groups of food (other than caffeine and alcohol) unless a very specific food trigger has been identified [22]. Studies on food-related triggers of headache in children and adolescents are few. Those which exist generally recommend avoidance of alcohol consumption and limited caffeine, as opposed to large-scale elimination diets [23–25]. Overall, a well-balanced diet with limited

caffeine intake and restriction on alcohol consumption is recommended. It is particularly important that practitioners assess regularity of meals, access to healthy foods, and food scarcity issues, as meal skipping is a well-known trigger for headache in the pediatric population [25]. Picky eating and irregular meal schedules due to school or activity schedules should also be assessed as areas of potential impact [26]. By recommending a well-balanced diet with regularly scheduled meals and limited caffeine intake, practitioners can address most of the potential barriers related to diet. If families and/or practitioners are particularly suspicious of a food-related culprit, a detailed food and headache journal kept for several weeks may help to identify specific triggers. In the relatively few cases where specific food triggers are identified, cheese, chocolate, citrus, hot dogs, monosodium glutamate, aspartame, fatty foods, and ice cream are common offenders in the pediatric migraine population [25].

Complementary/Alternative Treatments (CATs)

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a psychological intervention which is robustly established as an effective treatment for headaches in pediatric populations. Patients and families are often skeptical when psychological intervention is recommended for what they perceive to be a strictly physical concern. However, a great deal of evidence exists to support the use of CBT for a number of pain-related syndromes, including pediatric headache. Ernst et al. [27] describe CBT as having a "basic assumption that our thoughts, feelings, and behaviors are interactive and typically interdependent … CBT emphasizes the mind-body connection [and] highlights how natural and adaptive body processes (the stress response) may have gone awry, but can be restored through purposeful practice of evidence-based techniques that are directly related to target areas." For example, one common area of CBT intervention in pediatric headache involves challenging the automatic assumptions children and adolescents hold about their headaches and level of disability ("I have a headache therefore I cannot go to school") and teaching alternate ways of thinking, which result in better coping ("I have a headache so I will practice self-care and headache management before I leave for school"). CBT also often incorporates strategies for relaxation and stress management, which are strongly supported for headache management [28]. Several randomized controlled trials have confirmed the efficacy of CBT in children with headache, and benefits have been found to remain at least as long as 1 year, likely longer [29, 30]. Kroner et al. [31] compared children and adolescents with headache who were treated with CBT plus amitriptyline with those who were treated with headache education plus amitriptyline. A large percentage (47%) of the CBT + amitriptyline group were able to reach a frequency of headache days per month of four or less compared to 20% of the education + CBT group, with improvements maintained at 12-month follow-up. Table 9.4 illustrates the benefits of CBT in children.

Table 9.4 Established benefits of CBT [2, 28, 31, 32]

• Improved self-management of headaches • Improved adherence • Decreased headache frequency and severity • Improvement lasting beyond duration of treatment	• Decreased headache-related disability • Improved day-to-day functioning • Improved psychosocial adjustment • Decreased mood symptoms • Improved stress management skills • Improved school attendance (and decreased caregiver burden)

In addition to directly addressing headache-related thoughts and behaviors, CBT can also treat the psychological comorbidities which are extremely common in the pediatric headache population. There is a reciprocal relationship between mood concerns, such as depression and anxiety, and headache in children and teenagers. Among many commonly known risk factors, Kemper et al. [33] determined that depression presented the strongest risk for headache-related disability among adolescents. Children and adolescents with migraine are more likely to have somatic, anxious, depressive, social, attention, and internalizing symptoms as well as poorer psychosocial adjustment when compared to peers without headache [34, 35]. For patients with headaches that are stress related or exist in the presence of mental health concerns, a treatment approach that incorporates CBT can promote function and school attendance [26]. The presence of psychosocial indicators such as depression, anxiety, significant stress, and perception of family over involvement can be used to identify pediatric headache patients who would likely benefit from CBT [27].

Despite the well-established evidence base for CBT in pediatric headache, providers may find introducing this treatment option to families quite challenging. The unfortunate pervasive stigma of mental illness often results in families being immediately resistant to the idea of psychological intervention, preferring to focus on the medical or physical components of treatment. Children themselves may feel discounted or as though providers are telling them that their symptoms are "all in their head." Thus, it is crucial that practitioners have a good understanding of what CBT is and how it works to treat headaches. Early introduction is also important in order to normalize CBT and avoid the perception that CBT is a "last-ditch effort" when traditional medications are ineffective. Ideally, practitioners would have access to a psychologist trained in CBT for pain management embedded in the clinic, which further serves to destigmatize the intervention. However, we recognize that this practice is far from the norm. At the very least, practitioners should develop a resource list and relationships with psychologists in their area to facilitate referrals for appropriate treatment [27].

Biofeedback

Biofeedback is a training technique in which children and adolescents are taught to improve their health by using signals from their own bodies to regulate the autonomic nervous system. Biofeedback has a primary goal of increasing awareness of

physiological functioning and self-regulation of the stress response by using instruments that measure functions such as muscle tension, heart rate, respiration, and blood volume to provide real-time feedback to patients. Compared to controls, biofeedback can reduce frequency, duration, and intensity of headache symptoms and prevent headaches from occurring [36, 37]. It has been shown to improve headache symptoms with at least as much efficacy as many pharmaceutical agents in pediatric headache [37]. There are many advantages to biofeedback treatment, including short-term nature of intervention (8–12 sessions) and high response rate in children. Additionally, there is a lack of adverse effects. The highest efficacy rates for management of pediatric headache are associated with thermal (warming) and electromyography (EMG—muscle tension) biofeedback specifically. However, all modalities of biofeedback incorporate relaxation, and many biofeedback practitioners also utilize components of CBT in treatment. One significant drawback to biofeedback as a treatment for pediatric headache is the dearth of trained practitioners. In rural areas, this treatment modality may be one that is more difficult for patients to access.

Physical Therapy

Research on the benefits of physical therapy and spinal manipulation is mixed in pediatric headache, but anecdotal information suggests that many patients may benefit from physical therapy evaluation and treatment. One of the reasons it has been difficult to establish efficacy is the vast number of physical therapy techniques that can be used to treat headaches. Additionally, the need to individualize treatment makes conducting randomized controlled trials difficult. Small-scale studies indicate that manual therapy shows promise for headache, but more robust investigation is required [38]. The various modalities of physical therapy used in the pediatric headache population can include spinal manipulation, soft-tissue therapies, dry needling, postural education, muscle stretching, traction, and transcutaneous electrical nerve stimulation (TENS), among others. Cervical manipulation and mobilization are the most commonly used techniques for headache management [39]. Treatments vary across patients; there are no set protocols, given that each child has unique musculoskeletal needs which are addressed based on individual presentation and preference of treatment. It appears that children with accompanying neck pain and/or physical deconditioning may especially benefit from physical therapy. One particularly powerful set of advantages lies in the relatively easy accessibility and high rates of insurance reimbursement for physical therapy [39]. Anecdotally, we have found that many of our patients with uncontrolled headache and high levels of symptom-related disability benefit from manual physical therapy combined with structured reintroduction of physical activity under the watchful eye of a physical therapist who can help them pace activity appropriately. When practitioners conceptualize physical therapy as a CAT which can simultaneously decrease muscle tension and improve physical conditioning, it becomes an attractive adjunctive treatment which can help to address not only headache symptoms, but also overall health and wellness in pediatric headache patients.

Acupuncture

Acupuncture has increased in popularity in recent years as a treatment for a variety of physical concerns, particularly those which are pain related. There is scant research in Western medicine which addresses the benefit of acupuncture for headache, and even less that examines acupuncture in the pediatric population. Nonetheless, a Cochrane review of acupuncture in headache patients revealed a significant reduction in headache frequency for acupuncture patients when compared to those receiving routine treatment. Initial studies have indicated that six sessions of acupuncture can be helpful in addressing symptoms of tension-type headache and migraine [40]. Acupuncture appears to be most effective when combined with routine care, as opposed to when received as a solitary treatment [40]. Many pediatric patients are wary, as the practice of acupuncture is often novel and frequently anxiety provoking. Nonetheless, it is a reasonable option for patients who have poorly controlled headaches.

Yoga

Practices based on Eastern medicine and philosophy, such as yoga and meditation, have not been rigorously studied in the headache population despite anecdotal support. Despite the general dearth of research to support such practices, they bear mentioning due to their general popularity and ease of access. A few small-scale studies exist which, in general, support the idea that yoga and meditation may be helpful for those who suffer from headache and other pain-associated disorders. Yoga, even when practiced for short periods of time, may be effective in improving headache symptoms and quality of life [41, 42]. Meditation and mindfulness practice may be beneficial in regard to headache duration, disability, and self-efficacy [41]. While meditation and yoga may be more challenging for younger children, many adolescents may find these practices appealing due to the long-established link between yoga and stress reduction, as well as cultural popularity of the practice and easy accessibility through online videos.

Nutraceuticals

It is extremely common to encounter pediatric headache patients and their families who are quite strongly opposed to pharmacological intervention for headache management and who would prefer to explore options for nutraceutical treatment. Obviously, this approach comes with a number of challenges, not least of which includes lack of federal regulation of vitamins, minerals, and supplements, as well as relatively limited research in the pediatric population. Nonetheless, there is a growing body of research which supports the efficacy of specific nutraceuticals in

Table 9.5 Suggested nutraceutical dosing [44–51]

Nutraceutical	Child dosage	Adolescent dosage
B_2/riboflavin	200 mg daily	Up to 400 mg daily
Magnesium	200 mg twice daily	Up to 400 mg twice daily
Coenzyme CoQ_{10}	150 mg daily	Up to 300 mg daily
Melatonin	3–6 mg but may go higher	3–6 mg but may go higher
Feverfew	Starting dose 50 mg daily	

the treatment of headache. Because these substances are freely available to the public, and internet research does not always produce the most helpful (or safe) information, it is incumbent upon the pediatric practitioner to have a good knowledge base regarding nutraceuticals in the pediatric population in order to provide guidance and ensure the safety of patients. There are no official guidelines on the use of nutraceuticals specific to the pediatric population [43], and thus practitioners must extrapolate from adult guidelines and research across the life span, using good common sense to guide treatment. Table 9.5 notes several nutraceuticals with supportive evidence as a prophylactic treatment for headaches and migraines as well as suggested dosing.

Magnesium is one of the most rigorously studied supplements in the pediatric population and is commonly prescribed to children and adolescents. While research is mixed regarding its efficacy in treating acute headache symptoms, a prophylactic magnesium regimen has been found to decrease the number of headache days [44] and increase the efficacy of ibuprofen and acetaminophen [52] and is associated with very few side effects. Benefits of magnesium are sustained at 1-year follow-up [45]. Magnesium is thought to positively impact headache by supporting neuronal homeostasis and decreasing neuronal inflammation [53].

Riboflavin, also known as vitamin B_2, is another common supplement utilized in the treatment of headache. It plays a key role in cell membrane stability, mediation of oxidative stress, and energy-related cellular function [54]. It is one of the most commonly prescribed supplements for migraine treatment and has demonstrated level B evidence in preventing episodic migraine occurrence [46].

Coenzyme Q10 (CoQ10) acts as an antioxidant and has been shown to mitigate headache symptoms in the pediatric population [54], with level C efficacy [47]. It has been hypothesized that CoQ10 deficits may be common in children and adolescents with migraine. When patients with identified CoQ10 deficiencies received supplemental treatment, they demonstrated improvement in headache frequency and disability [48].

Butterbur is a shrub native to Europe and parts of Asia and North America. It was shown to exert promising effects on headache in children but was withdrawn from the American Academy of Neurology guidelines due to risk of hepatotoxicity. Butterbur works by inhibiting leukotriene synthesis, regulating calcium channels, and exerting anti-inflammatory effects [55]. Despite its positive effects, patients and families should be directly and strongly discouraged from utilizing butterbur as a treatment option due to its potentially life-threatening side effects.

Feverfew is a plant-based supplement that is one of the most rigorously studied prophylactics in the treatment of adult migraine. However, it has not been well studied in children and adolescents; thus, long-term safety has not been established in the pediatric population [43, 49]. Feverfew demonstrates level B efficacy (probably effective) in the adult population [47].

Melatonin, while generally associated with sleep, has been indicated for headache prevention in general and thus allows practitioners to address two common concerns at once. While the evidence base is broadest in the adult population, Gelfand et al. (2020) determined that in adolescents and children, both low- and high-dose melatonin can be effective in the acute management of pediatric migraine [50, 56]. Further, small-scale studies in children and adolescents demonstrate preliminary efficacy of melatonin in the preventative sense [51].

Summary

The successful assessment and treatment of pediatric headache involve far more than the headache itself. It is crucial that practitioners understand the need for broad-based assessment of the whole child and family before prescribing any one treatment modality. Prescribing pharmacological intervention without considering lifestyle and psychosocial factors is likely to be unsuccessful and may lead to unnecessary medical intervention, increased headache-related disability, and increased family burden. Practitioners are encouraged to "think outside the box" of medical intervention to identify appropriate lifestyle interventions and CATs, which can supplement traditional treatment. Many CATs address multiple factors which contribute to headache presentation and thus can produce benefits to the well-being of the pediatric patient across physical and psychosocial domains. The pediatric practitioner is encouraged to use the information contained in this chapter to supplement the physical examination and assessment in order to have the highest likelihood of successful treatment.

Return to Case 1

Now that we have examined a number of lifestyle factors, CATs, and nutraceutical intervention for pediatric headache, let us return to our case vignette to examine how these interventions may benefit Alice. Recall that Alice is a 16-year-old female with recurring headaches and several contributing lifestyle factors. Based on her presentation, Alice was diagnosed with **migraine without aura**, and the following was recommended:

- **Increased hydration, with the goal of 8–9 urinations per day**
- **Age-appropriate sleep hygiene, including elimination of naps, gradual shift of bedtime, and utilizing relaxation to aid sleep onset**
- **Regular meals and avoidance of caffeine**
- **Aerobic activity of 30 min/day at 3–4 times per week**
- **Stress management and CBT**

Prophylactic, abortive medications, and nutraceuticals were discussed with the family at their initial clinic visit, but the family preferred to focus on lifestyle recommendations before beginning any type of pharmacological or nutraceutical intervention. Alice consulted with the clinic psychologist for CBT and strategies to incorporate the above recommendations. At 1-month follow-up, Alice's migraines had reduced in frequency from twice weekly to thrice monthly, and she was prescribed a triptan for abortive management of migraines when they occur.

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Chapter 10
Prophylactic and Acute Pharmacology for Pediatric Headache

Alma R. Bicknese

Introduction

It is an interesting time for headache medicine. We have greater understanding of the underlying pathophysiology leading to several new headache treatments that have changed headache management. With advancements, these newer options have been more readily studied in the adult population and as such used more widespread in this population. Pediatric use is following, especially as more pediatric and adolescent studies are completed, but will take time to gain traction.

The reason for the excitement regarding the future of headache management stems from two areas of advancement in headache management. The first is a new, better understanding of the role of the trigeminal system and the release of calcitonin gene-related peptide (CGRP) in migraine propagation [1]. The other area of advancement has been improved understanding of how environment and behavior affect migraine. What is interesting is that the power of environment and behavior appears to affect children and adolescents even greater than adults. It can be difficult to demonstrate therapeutic efficacy in children when they have a high spontaneous remission rate and placebo response [2, 3].

When considering the history of headache pharmacology, the beginnings date back to the vascular or Wolff theory of migraine (headache) that was the dominant theory of headache pathophysiology for most of the twentieth century and directed therapeutic attempts at both acute and prophylactic pharmacology options for headaches, and more specifically migraines [4]. When considering migraines specifically, they were thought to have two phases. The first phase or prodromal phase was vasospasm, which caused focal cerebral ischemia and transient neurologic

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symptoms like visual aura. The second or headache phase was vasodilation of both the intracranial and extracranial blood vessels. As they dilated, this produced pounding pain [4].

The first medications studied and used in the early twentieth century were those containing ergots, as they were potent vasoconstrictors that were thought to improve headache by constricting the dilated blood vessels. As time went on, the prevention of headache and migraine focused on medications that are active in the vascular system based on this early understanding of headache pathophysiology, with the most common preventative beta-blockers like propranolol and calcium channel medications like verapamil. The use of antidepressants, namely tricyclic antidepressants such as amitriptyline, has also been a mainstay of therapy, although these never really fit into the vascular theory and were thought to work by modifying central pain or improving mood [3, 4].

In the 1990s, the neuronal theory of migraine became a prominent view of headache pathophysiology, where it was thought that migraine and migraine aura were caused by paroxysmal depolarizations of cortical neurons [5]. This led to trials with cortically active medications best exemplified by anticonvulsants such as topiramate, along with the nutraceuticals such as magnesium, which are still in use today as commonly used prophylactic agents in the treatment of pediatric headache. During this time period, the mainstays of migraine prevention remained antidepressants (as mentioned above), antihypertensives (as mentioned above), and anticonvulsants [2, 3, 5]. In the 2000s, the neurovascular theory became the dominant pathophysiology theory for headache and migraine. Migraine is primarily a neuronal problem with vascular components. Under this theory, migraine brains are chronically hyper-excitable and, when triggered, generate the migraine and aura, which in turn affects blood flow to the brain. This model accepts both vascular and cortical therapies [6]. Botulinum toxin and CGRP modulators arose during this era and have become part of the wide-ranging prophylactic options with building support that are available for those suffering from recurrent headaches, including migraine, one of the most common yet disabling headaches seen in the pediatric population.

Of note, much of the inflammation is mediated by calcitonin gene-related peptide (CGRP) which, when released, triggers a cascade of inflammatory mediators that feed into the trigeminovascular system. Blocking CGRP with medications or by inhibiting the trigeminal system from releasing CGRP improves migraine [7]. It is this understanding that makes the future of pediatric headache management so bright and intriguing given the advancements in the understanding of headache pathophysiology, thus leading to new treatments, both prophylactic and acute that target CGRP (to be discussed below and in Chap. 12).

It is believed that children have the same migraine pathology as adults and as such should respond to the same classes of medications. Drug trials have been difficult to perform in children because of concerns over administrating medications to children and because the placebo response rate is so much higher in children. In numerous studies, the placebo response is between 40 and 60% [8]. It is very difficult to prove that a therapy is effective with such a large placebo response. To

overcome these issues, a large multicenter study was needed. The CHAMP trial was the first large multicenter study comparing the two most widely used migraine preventatives in children: amitriptyline and topiramate to placebo [3].

There had been concerns about whether a large trial could be done in children, but this study shows that it is feasible. The format was standard methodology common in adult trials. The children enrolled and documented their headache frequency for 3 months and then began the active arm of the study. Headache baseline in all three groups was unchanged until the active arm of the study began. All three arms of the study including placebo arm showed a significant improvement from baseline. Amitriptyline's improvement was matched by placebo. Topiramate showed a slight nonstatistical improvement compared to placebo, which could possibly indicate the potential to be superior to placebo [3].

Why was the placebo response so large, and how does this affect our clinical practices?

Would any treatment that the family believes is an active result in a significant number of children reporting less pain? If so, one could argue that prescribing any medication or even a placebo would work in a significant number of children. In fact, physician surveys indicate that many do prescribe medications at a lower dose than expected to be therapeutic as a placebo treatment [9]. While this conclusion is logical given the study results, it does not align with clinical observation (e.g., no one argues that prescribing antibiotics helps migraine or tension headaches and as such is not routinely done).

The answer likely lies somewhere in the middle where a combination stepwise multitiered treatment approach focuses on daily lifestyle modification and triggers avoidance, offering complementary and alternative therapies and initiating prophylactic treatment (nutraceuticals and/or pharmacology) when warranted. As such, another consideration is that the study overlooked confounding variables that caused all groups to improve. To standardize the patient response, all study sites agreed to the patient experience based on what were believed best practices at the central institution. Patients were taught how to maintain headache diaries, track for food and activity triggers, and optimize sleep, fluid intake, and meals. Patients were instructed to use their acute medications early in the attack rather than waiting to see how bad the headache was. Their acute pain medications were at standardized dose for weight [3]. Because this was considered standard management, there was not a control group who were left to their own devices. They did not study whether improving management alone helped headaches. It could be that this management alone accounted for much of the improvement in all groups, enough to mask any effect from medication.

There have not been any prospective natural history studies of headache in children. It is entirely possible that many children's headaches improve much faster than adults and that many would have naturally improved over the study period. If so, any effect of the medications would have been masked. It may be logical then to wait a few months before offering medications to all headache patients, but this is a fine line as waiting too long or dismissing their headaches may lead to worsening long-term dysfunction and disability as the patient ages and transitions to adulthood.

Another important consideration when differentiating between pediatric and adult headaches is school. The natural history of pediatric headache is strongly influenced by the school year. In the United States, nearly all children are out of school and at home for a continuous 10–11 weeks for summer vacation. Many providers who see pediatric headache patients will describe a yearly pattern where headaches improve during the summer break and begin returning in the fall after the start of school. It is possible that the expected seasonal improvement in headaches masked treatment effect. This is also an important factor to consider while deciding to change treatments whether it be escalating treatment by changing or adding prophylactic options or de-escalating treatment by weaning or discontinuing prophylactic agents.

CHAMP study has had a strong influence on clinical practice and will continue to shape the future of the prophylactic treatment of pediatric headache. The most recent pediatric headache practice parameter for pharmacologic treatment to prevent migraine states that medications have failed to demonstrate superiority to placebo [10, 11]. Migraine prevention has shifted from primarily prescription medications to an approach including a multitiered approach that incorporates lifestyle and behavioral factors along with pharmacology.

As such, preventing or decreasing headaches and migraines is more than prescribing medications (discussed in greater detail in Chap. 9). Before turning to prescription medications, the multiple behavioral factors affecting migraine should be addressed. First management should include a careful lifestyle and behavioral history followed by addressing how behavior affects migraine. In adolescents, poor sleep, lack of physical activity, and caffeine and alcohol use are associated with higher headache disability. If these underlying factors are not addressed, pharmacologic management will not be successful. Encouraging water intake improves headache, with teens recommended to drink greater than 1.5 L or 64 oz. of water during school [12]. Every child should leave with a home and school plan addressing exercise, meals, sleep, and water intake [12, 13]. If these are not addressed, it is unlikely that pharmacologic management will be successful.

For many children, addressing these lifestyle and behavioral factors will decrease headache frequency enough that a prescription preventative may not be needed. Table 10.1 is an example on "prescribing" lifestyle and behavioral changes that can be checked off and/or followed up at subsequent return visits. School-age children may need a provider's letter, order, or possibly a 504 plan to help with

Table 10.1 Lifestyle and behavioral changes for pediatric headache/migraine

Recommendations on improving headache	Accomplished
Regular sleep (general rule 8+ h uninterrupted at night)	
Regular meals and snacks (general rule eat breakfast, lunch, and dinner daily)	
Regular exercise (general rule 1 h a day, minimum 20 min a day)	
Limit caffeine	
Increased fluid intake (general rule 16 oz. every 2 h)	

recommended daily lifestyle changes during the school day. Recommendations may include, but not limited to, being able to carry water and/or snacks into the classroom and having allowances for extra bathroom breaks.

Case

14-year-old averaging one migraine headache a week. Most start in the afternoon while at school or on the way home. He has not missed school because of the headaches but has missed several after-school events. If they start at home, he takes acetaminophen or ibuprofen but only 200 mg. Otherwise, he sleeps them off. He generally goes to bed at around 11:30 or 12 a.m. and awakens at 6 a.m. to catch a bus. He usually gets up too late to eat breakfast but eats lunch and dinner. He gets something to drink at lunch but avoids using the drinking fountains so otherwise may go most of the day without water. He finishes his homework late and then goes to his room where he socializes with friends and plays games online. He and his family are given advice on increasing sleep so he is less tired in the morning and can eat and drink before school. In addition to a prescription of 10 mg/kg ibuprofen, he is given a letter allowing him to carry water and keep a bottle at his desk and have extra bathroom breaks. On follow-up, his headache frequency has dropped to an average of one every 6 weeks.

Pediatric Headache Preventative (Prophylactic) Treatments

Many children have significant disability from migraine and should be considered candidates for prescription preventative medications. We know that adults with headache more than 6 days a month are at risk to progress from episodic to chronic migraine [14]. Once headaches are approaching this cutoff, the physician should consider discussing a preventative.

Many with frequent headaches will also develop medication overuse, worsening the progression to daily to near-daily headaches [15]. When the use of triptans approaches 9 days a month, and over-the-counter analgesics more than 14 days a month, the problem of MOH should be addressed with the patient and family, and addition or adjustment of a preventative medication is reasonable.

Nutraceuticals for Pediatric Headache Prevention

Many pediatric headache practitioners have begun prescribing nutraceuticals (vitamins, minerals, and plant materials) first line before pharmacologic medications. There are placebo-controlled studies in adults supporting several supplements. With the lack of pediatric migraine preventative studies showing medication superiority, it may be reasonable to start with a nutraceutical. Nutraceuticals are reviewed in more details in Chap. 9 but will be reviewed here as well.

Several nutraceuticals are commonly used in the prevention of pediatric headache and migraine. The limited studies using riboflavin, magnesium, and coenzyme Q10 are at the same level of scientific proof as many prescription preventatives [16–19]. Recognizing that there is some evidence for efficacy and that these can be introduced along with the behavioral and lifestyle changes does make them an appealing first preventative in clinical practice. Additionally, other options as previously discussed in Chap. 9 are also available and have support including feverfew, butterbur, and melatonin. Of note, proprietary supplements are available that compound 2–4 nutraceuticals into a single capsule making dosing easier. Several of these proprietary capsules have prospective observational data showing efficacy but without placebo controls.

Case

9-year-old averaging 5 migraine headaches a month. Most start at school or baseball practice. She gets 9 h of sleep, eats regular meals, and is physically active. She drinks at lunch and but seldom uses the drinking fountains. They express reluctance to "medicate" their child. After discussion, there is agreement that the child will be allowed to take ibuprofen 10 mg/kg at headache onset and carry water at school with a goal of emptying a water bottle before and after lunch. The family begins a compound with riboflavin, magnesium, and feverfew at night. On follow-up, her headaches have decreased to one a month, and the headache responds quickly to ibuprofen.

Prescribing Preventative Medications for Pediatric Headache

Children with headaches in or above 5–6 days a month category should be considered for prescription medications. These children are at risk for developing chronic daily headache and medication-overuse headache. A medication trial should be at least 6 weeks at a therapeutic dose before considering it a failure. When starting a medication trial, counsel the family that results may take several months, if not longer, for the effects to become evident. Currently, there are no preventative medications with established efficacy in children under 12 years of age, and only topiramate has approval for headache or migraine prevention in the adolescent population. The 2019 American Academy of Neurology pediatric practice guideline acknowledges the lack of good studies in children [2]. The guidelines list propranolol, amitriptyline, and topiramate as probably therapeutic. The positive amitriptyline studies were done along with cognitive behavioral therapy, so independent effectiveness has not been established [20]. While other prophylactic pharmacological agents were not specifically noted, there are many other medications that are often used in the prevention of pediatric headaches or migraines (see Tables 10.1 and 10.2). For most primary care providers, it is recommended that they become familiar with a few of the below options to offer their patients and families should headache prophylaxis be warranted (see Table 10.2).

Table 10.2 Efficacy score of pharmacologic agents used for headache/migraine[a]

Medication	Pediatric guideline	Adult guideline	Efficacy score
Beta-blockers			
Propranolol	Probably effective	Established efficacy	5
Metoprolol, atenolol, and timolol	No information	Established efficacy	3
Carbonic anhydrase inhibitors			
Topiramate	Probably effective	Established efficacy	5
Zonisamide	No information	No information	0
TCAs			
Amitriptyline	Probably effective (with cognitive behavioral therapy)	Probably effective	4
Nortriptyline	No information	No information	0
Sodium valproate	No information	Established efficacy	3
CGRP inhibitors (e.g., fremanezumab, erenumab, galcanezumab)	No information	Established efficacy	3
Botulinum toxin	No information	Established efficacy	3
SNRI			
Venlafaxine	No information	Probably effective	2
Duloxetine	No information	Probably effective	2
Cyproheptadine	No information	Possibly effective	1
Gabapentin	No information	Conflicting information	1

TCA tricyclic antidepressant, *CGRP* calcitonin gene-related peptide, *SNRI* serotonin and norepinephrine reuptake inhibitor

[a]Treatments listed are used for headache prophylaxis. Not all options listed are approved for headache/migraine prevention but are used nonetheless; topiramate is the only approved headache/migraine preventative in pediatrics (12 years or older). Most options used in pediatric headache prophylaxis are considered off-label use. Studies may be ongoing for some agents, and as such this information may change over time

Despite this, practitioners continue to prescribe a variety of oral medications for pediatric headache and migraine prophylaxis, many of which have been shown to be effective in the adult population and being used with a trickle-down mindset as noted above. This is justified if one accepts that childhood migraine is a similar illness as adult migraine with the same pathophysiology. Perhaps the difficulty in designing a good pediatric study has prevented proof of efficacy; but nonetheless, it would be unfair to deny children with a chronic and often disabling medical problem the same medical options as adults simply due to an opacity of studies and evidence in their specific population.

Additional considerations should be considered for children and adolescents. There are Food and Drug Administration (FDA) warnings about suicidal thoughts and behavior with antidepressants including those that are commonly used as a headache prophylactic treatment, and this must be discussed with the child and

family. Adolescent women of childbearing age should be advised that many commonly used options such as valproate/divalproex should not be used in pregnancy due to harmful effects, including possible teratogenic effects, and as such caution should be used in those who are sexually active and/or may be pregnant [2].

Given the wide-ranging options as well as special considerations when determining the medications to prescribe, Table 10.2 may be helpful in deciding which medications have the best evidence of efficacy (3 points for proven efficacy, 2 for probable efficacy, 1 for possibly effective and mixed information). Table 10.3 provides commonly used prophylactic pharmacologic agents for pediatric headache with how to initiate, titrate, and monitor before and during usage.

Table 10.3 Commonly used preventative medications for pediatric headache/migraine in primary care

Medication	Monitoring	Starting dose	Titration	Goal dosing	Special consideration
Amitriptyline	EKG prior to initiation and at goal dose (QT prolongation)	0.1 mg/kg QHS, typically 10–25 mg	Increase every 2 weeks by 10–25 mg	1–1.5 mg/kg QHS Upper target: 100 mg QHS	Caution regarding suicide ideation and overdose. Do not use with prolonged QT
Cyproheptadine	None routinely	0.25 mg/kg QHS, typically 2–4 mg	Typically not done but can be 2–4 mg as tolerated	4–8 mg QHS but can go higher as tolerated (including morning dosing)	Caution regarding obesity and oversedation Often first-line option in migraine precursors
Gabapentin	None routinely	Typically 100–300 mg QHS	Increase every 1–2 weeks by 100–300 mg; once at 10–15 mg/kg QHS may need to add morning dose	1200–1800 mg divided 2–3 times a day but can go higher as tolerated Upper target: 30–35 mg/kg/day divided 2–3 times a day up to 3600 mg/day	Caution regarding sedation, especially when adding daytime doses and/or titrating to higher doses
Propranolol	Vitals (looking for hypotension or bradycardia)	Typically 20–80 mg divided 2 times a day (can be daily with extended release)	Increase every 2 weeks by 20–40 mg per day	0.6–3 mg/kg/day Upper target: 80–120 mg/day but can go higher as tolerated	Caution with bradycardia or hypotension, asthmatics, or those with depression

Table 10.3 (continued)

Medication	Monitoring	Starting dose	Titration	Goal dosing	Special consideration
Topiramate	None routinely but may follow BMPs	Typically 25 mg QHS	Increase every 2 weeks by 25 mg; once at 50 mg QHS can add morning dose with subsequent titrations	3 mg/kg/day divided 2 times a day but can go higher as tolerated Upper target: 100–200 mg/day divided 2 times a day	Do not use in pregnancy; caution with concomitant use of hormone-based contraceptive—may diminish effectiveness and see breakthrough bleeding; other contraception recommended if sexually active

Goal/target dosing may be higher in adult patients and not typically weight based. Side effects and other factors/considerations in tables
EKG electrocardiogram, *mg* milligram, *kg* kilogram, *QHS* nightly, *BMP* basic metabolic panel

Case

An 11-year-old is seen in follow-up for migraine headaches. At his last visit, the family applied behavioral and lifestyle changes including sleep and regular meals and has been meeting water goals. They have been giving magnesium daily. His headaches have improved, but he still has about one headache a week. He is placed on propranolol twice a day. At the next follow-up, his headaches have decreased to about once a month.

In addition to the evidence of efficacy, ease of use and side effects influence which medications are chosen. The medications most often used by pediatric headache providers are in part based on common practice patterns. For instance, cyproheptadine is widely prescribed in children with little published data showing that it is effective and no placebo-controlled studies in either pediatrics or adults. Many clinicians find it helpful to classify by side effects and whether available in liquid or tablet. Table 10.4 gives commonly used prophylactic medications for pediatric headache with which patients may be more appropriate for each treatment along with similar options that may be used as substitutes based on side effects, tolerability, ease of use or formulation, and insurance coverage or cost. Of note, many medications can be found or compounded into liquid preparations for those who are unable to swallow pills. Additionally, many options, or a similar alternative, come in a once-daily dosing option to aid with medication compliance.

Patient Examples

- A 15-year-old male athlete with average BMI would be a good candidate for valproate, could be considered for topiramate, and should avoid propranolol.
- A 16-year-old of either sex with fibromyalgia and obesity would be a good candidate for duloxetine or gabapentin, could be considered for topiramate, and should avoid amitriptyline, valproate, and cyproheptadine.

Table 10.4 Considerations for pharmacologic agents used for headache/migraine

Medication	Recommended in	Avoid in or use with caution	Potential side effects	Alternate medication
Propranolol	Hypertension, POTS, tremor	Asthmatics	Depression, sports performance	Metoprolol or other beta-blockers
Amitriptyline	Thin children, children with insomnia, comorbid irritable bowel syndrome	Obesity, psychiatric conditions, constipation	Sleepiness, weight gain, suicidal ideation, constipation, anxiety	Nortriptyline or other TCA
Topiramate	Overweight, those with epilepsy	Underweight, potential for pregnancy	Sleepiness, decreased appetite/weight loss, brain fog/ cognitive concerns, metabolic acidosis, paresthesia	Zonisamide
Valproate	Thin children, males, those with epilepsy	Females of childbearing age, obesity, liver disease, blood disorders	Weight gain, polycystic ovary disease, blood and liver disorders, hair loss, teratogenic	None
Cyproheptadine	Underweight children, comorbid GI disorders	Obesity—High risk	Excessive weight gain, sleepiness, and sedation	None
Gabapentin	Chronic pain disorders like neuropathy or fibromyalgia	Few contraindications	Sleepiness and sedation	Pregabalin
Duloxetine or venlafaxine	Chronic pain disorders like fibromyalgia, anxiety, OCD, PTSD	Psychiatric conditions	Suicidal ideation, anxiety, depression	Venlafaxine or duloxetine other SNRIs
Botulinum toxin	Failed other preventatives	Procedure, requires referral to administering provider	Transient facial weakness	None
CGRP inhibitors (fremanezumab, erenumab, galcanezumab)	Failed other preventatives	Difficult insurance approval	Occasional constipation Site reaction at injection site	Alternate CGRP inhibitors

POTS postural orthostatic tachycardia syndrome, *TCA* tricyclic antidepressant, *OCD* obsessive-compulsive disorder, *PTSD* post-traumatic stress disorder, *SNRI* serotonin and norepinephrine reuptake inhibitor, *CGRP* calcitonin gene-related peptide

- A 10-year-old child who is underweight and with chronic abdominal pain would be a good candidate for cyproheptadine or amitriptyline and should avoid topiramate.
- A 13-year-old with mild anxiety would be a good candidate for propranolol or topiramate. Duloxetine, venlafaxine, and amitriptyline are antianxiety medications and are often used for children with comorbid anxiety. If prescribing antidepressants, the children need to be monitored for suicidal ideation or worsening anxiety or depression.

Summary for Prophylactic Treatment for Pediatric Headache

Children with frequent migraine headaches should be offered therapies that prevent or decrease their headache frequency. Migraine disability significantly worsens when headache frequency rises to 6 or more a month. With these many headaches, many will develop MOH, making acute therapy more difficult [14, 15]. All children should be taught behavioral and lifestyle practices that can worsen or improve headache frequency. It is reasonable to consider nutraceuticals as a preventative, but if used and headaches do not improve within a few months, do not hesitate to prescribe a prophylactic medication at appropriate dosing. Most preventatives take several months to be fully effective, and families should be warned that it might take that long to see a benefit.

While it is reasonable to consider amitriptyline, topiramate, and propranolol as first-line options as these are noted in the most recent pediatric headache/migraine practice guideline [2], it is important to remember that there are many other options available. Of note, it is important to be mindful that the majority of those options available, including some of those noted in the guidelines, are not approved for use as a pediatric headache prophylactic and as such most treatments are off-label. Given this along with what the limited available studies have shown (see above), it is recommended that when choosing a preventative agent the whole child be considered including thinking about comorbid conditions, other treatments already in place, side effects, and feasibility of the proposed treatment.

Acute Pharmacology for Pediatric Headache

Once a specific headache diagnosis such as migraine is determined, an individualized acute treatment plan should be outlined for every patient [13]. Migraine, specifically, responds best to early management with significantly higher pain-free rates when treated in the first hour. Families, and patients alike, should be taught that the longer one waits to treat, the less likely they are to see a beneficial medication effect [21]. This is different than tension headache, which often responds the same throughout the headache. In school-age children, an acute headache plan for home and school should

Table 10.5 Analgesic agents Used in the treatment of pediatric headache/migraine

Medication	Pediatric practice parameter	Dosage	Notes
Acetaminophen	Yes	10–15 mg/kg/dose every 4–6 h	Often ineffective in teens and adults but can be effective in younger children
Ibuprofen	Yes	10 mg/kg/dose every 6–8 h	Dose by weight. Package instructions usually underdose
Naproxen sodium	Yes[a]	5–7 mg/kg/dose every 12 h	May be less likely to induce MOH
Diclofenac potassium	No	50–100 mg/dose every 12 h	Recommended for teens and adults. May be less likely to induce MOH
Celecoxib	No	100–200 mg every 12 h	May be useful for some medical conditions like bleeding disorders
Ketorolac	No	0.5 mg/kg/dose up to 30 mg IV every 6 h 0.5 mg/kg/dose IM every 6 h (higher doses may be considered) 10 mg oral every 6 h	Often used as part of acute combination treatment in provider's office, urgent care, or emergency department Oral dosing is more often used in older adolescents

mg milligram, *kg* kilogram, *MOH* medication-overuse headache, *IV* intravenous, *IM* intramuscular
[a]Naproxen alone has not been studied in pediatric migraine. Studies were done with a proprietary compound with sumatriptan [23]. Naproxen has class A evidence in adults

be part of initial management. For migraine, it is important that therapy start even at school during the "golden" hour while there is a good chance of controlling, and hopefully eliminating, the pain. Waiting until a child gets home may result in prolonged headache and could have a higher impact on migraine disability.

When considering migraine, it is important to remember that it is a complex disorder, and along with pain, a migraine may also include symptoms of aura, light and sound sensitivity, and nausea or vomiting. Aura is self-limited and does not require acute treatment typically, but it is worth noting that prolonged aura may present and can be hard to identify, especially when it is not followed or accompanied by a headache itself. Nausea and sensory sensitivity, however, can be debilitating and should be managed as aggressively as pain. In many migraine patients, a combination approach may be necessary, and as such several classes of medications including those specific to nausea could be offered as part of the acute migraine treatment plan. To use a music analogy, the analgesic agents, including nonsteroidal anti-inflammatory drugs, are the bass, and the triptans and anti-nausea medications are the treble [22]. Table 10.5 identifies commonly available and used analgesic agents that are often used as a first-line option or as part of a combination approach to treat pediatric headache and migraine.

Acetaminophen and ibuprofen are widely available in liquid or chewable forms, and most parents are comfortable using these. The over-the-counter instructions are age based and often underdose. Parents should be given the mg/kg or "headache/migraine dose." Naproxen, diclofenac, and celecoxib have longer half-life and may

be more effective in children with longer headaches or headaches that recur on the same day. These may be less likely to induce medication-overuse headaches and may be considered before ibuprofen or acetaminophen if headache frequency is approaching 15 days per month. Ketorolac is more often used as part of acute treatment combination therapy administered in a medical setting but can be used at home in oral form in some patients where other analgesics have not been effective. What is important to remember about simple analgesics with regard to treating pediatric headaches is that when they are used appropriately, with respect to timing and dosing, they are often very effective and may be all that is needed to treat most acute headache attacks.

Case

6-year-old with migraine every 3–6 weeks. The family has tried Tylenol and ibuprofen without effect. You discover that they have been underdosing based on age-based dosing instructions. You suggest ibuprofen 10/mg/kg/dose. On follow-up, this is effective for nearly all headaches.

When analgesics are not effective, other options are available to be used in place of or in combination with analgesics. Triptans are one such option that may be used in pediatric headache, namely migraine, by working on the 5-HT1B/1D serotonin receptors. Triptans have an interesting backstory that goes back to the original treatments studied in the treatment of migraine. Ergot alkaloids were noted to cause vasoconstriction and were also effective in migraine. This fits with the dominant migraine theory of the time of vasoconstriction followed by vasodilation causing migraine pain. Triptans were developed as a safer alternative. In fact, triptans do not work via vasoconstriction but rather prevent the release of CGRP by neurons [24, 25]. Any vasoconstriction is an unwanted side effect. Most recent studies show that triptans have minimal vasoconstriction at therapeutic dosing. Recent studies have proven triptans to be both effective and safe in pediatrics. Triptans should be avoided with cardiac accessory conduction defects like Wolff-Parkinson-White syndrome. If one triptan fails, another may be more effective [10, 21–23].

Triptans (see Tables 10.6 and 10.7) are available in tablet or oral disintegrating tablet (ODT) for those who cannot swallow pills. Nasal spray forms have faster action, but many children refuse to use them because of their bitter taste or use them incorrectly. Injectable sumatriptan has a high efficacy, but many parents, as well as patients, are reluctant to inject their children or themselves, even in the midst of a migraine. In general, it is typically recommended to start with oral and advance to spray or injection only if needed. Exceptions may be needed for nocturnal headaches or headaches with excessive vomiting. Triptans are most effective in the first hour of headache. Triptans can be tried later, but after 2 h have lower efficacy.

Case

13-year-old with migraine once or twice a month. They report about half response to ibuprofen. You increase the ibuprofen to 10 mg/kg/dose and add in sumatriptan 50 mg as acute medications. His plan is to take the ibuprofen and if the headache persists follow it with the sumatriptan. The family calls and reports that his

Table 10.6 Oral triptans

Medication	Pediatric guideline	Dose (mg)	Half-life (hr)	Formulation	Comments
Sumatriptan	Yes	25, 50, 100	2	Tablets	25 mg as effective as placebo, 50 and 100 mg are likely effective
Sumatriptan with naproxen (Treximet)	Yes	10/60 30/180 85/500		Compounded tablet	Higher doses are more effective (many practitioners prescribe naproxen and sumatriptan as separate prescriptions taken together rather than using as a formulation)
Rizatriptan	Yes	5, 10	2	Tablet and ODT	Likely effective
Almotriptan	Yes	6.25 12.5 25	3.5	Tablet	6.25 mg as effective as placebo, 12.5 and 25 mg likely effective
Eletriptan	Yes	40	5	Tablet	Likely effective
Zolmitriptan	No	2.5 5	3	Tablet and ODT	Pediatric trials were negative
Naratriptan	No	1 2.5	6	Tablet	Pediatric trials were negative Sometimes used for menstrual migraines
Frovatriptan	No	2.5	25	Tablet	No pediatric trials. Sometimes used for menstrual migraine

mg milligram, *h* hour, *ODT* oral disintegrating tablet

Table 10.7 Nasal and injectable triptans

Medication	Available dosages	Notes
Sumatriptan nasal	5 mg, 20 mg	Recommend using 20 mg for most patients
Zolmitriptan nasal	5 mg	
Sumatriptan injectable	4 mg and 6 mg	6 mg recommended for adults and adult-size pediatric patients

mg milligram

headaches do not always respond to treatment and he is still missing activities. You discover that the family has been waiting several hours to give the sumatriptan. They are told to give the sumatriptan and ibuprofen together at the start of the headache. They report that this is much more effective.

Case

15-year-old averaging 3 migraines a month. He has failed ibuprofen 10 mg/kg. You prescribe rizatriptan 10 mg at the onset of migraine. He now gets headache relief in about half his attacks. He is converted to sumatriptan/naproxen 85/500 mg, which is usually effective if taken immediately.

The clinical trials using a fixed naproxen to sumatriptan dose demonstrated better efficacy than either medication alone [23]. These were the only studies with dual management of a triptan and a nonsteroidal at headache onset. Given the difficulties in performing such studies, it may be some time until other medication combinations are studied. It is common practice to try a nonsteroidal first and add in a triptan if needed. Less often a triptan will be tried first and a nonsteroidal added in if needed. It is often less costly to prescribe the triptan and the nonsteroidal separately than the compounded tablet, and prescribing separately will allow more flexibility in medications and dosing. What is key to remember is that combination is typically recommended, as noted in the most recent pediatric migraine treatment guidelines [10].

Sumatriptan and zolmitriptan are available as nasal sprays. Adult studies show faster onset of action and higher response rates than tablet, but pediatric studies have not shown these to be more effective than placebo [22]. Many children find the nasal sprays unpleasant and will not use them. Nasal triptans may be considered first line in select cases such as nocturnal migraines where the spray can be kept at bedside and used upon awakening. Sumatriptan is available in injectable formulation and can be considered if oral or nasal forms have failed.

Case

16-year-old with one or two migraine headaches per month including some with nocturnal onset that awaken him from sleep. Most headaches respond to oral ibuprofen and rizatriptan, but the nocturnal headaches do not. He is prescribed 20 mg nasal sumatriptan and uses this successfully for the nocturnal headaches.

Nausea and/or vomiting are major migraine symptoms that frequently do not respond to either analgesics or triptans. In some cases, it may prevent the patient from taking oral medications at all or from giving the medication time to be absorbed and thus effective. Many children will need an antiemetic (see Table 10.8) with some or all their headaches [10]. There are no dedicated clinical trials specifically evaluating antiemetics for pediatric migraine. Many practitioners will use ondansetron, a 5HT3 antagonist, initially as there are fewer potential side effects. However, antidopaminergic agents, such as prochlorperazine and metoclopramide, are likely more effective in the acute treatment of migraine as they not only work as an antiemetic but

Table 10.8 Antiemetics used in migraine

Medication	Available formulations	Notes
Ondansetron	Oral solution, tablet, ODT, IV	Theoretical interaction with triptan yet still often used
Metoclopramide	Oral solution, tablet, ODT, IM, IV	Multiple medication interactions, may induce dystonia or tardive dyskinesia (diphenhydramine can be used to treat/prevent SE)
Prochlorperazine	Oral solution, tablet, IM, IV, suppository	Multiple medication interactions, may induce dystonia or tardive dyskinesia (diphenhydramine can be used to treat/prevent SE)

ODT oral disintegrating tablet, *IV* intravenous, *IM* intramuscular, *SE* side effects

Table 10.9 Gepants and ditans

Medication	Available dosages	Notes
Ubrogepant	50 and 100 mg tablets	Strong CYP3A4 inhibitor, no pediatric studies
Rimegepant	75 mg tablets	No pediatric studies
Lasmiditan	50 and 100 mg tablets	No pediatric studies

mg milligram

can also directly combat the migraine attack itself through their work as dopamine antagonists as well as antihistamines, anticholinergics, and certain serotonin receptor blockers. Prochlorperazine and metoclopramide can be used as part of a combination treatment approach for migraines or as an independent individual migraine treatment as they work on both associated symptoms and migraine pain.

Case

7-year-old with migraines every 4–6 weeks. If he treats them early enough with ibuprofen 10 mg/kg, they respond, but about half the time, he progresses to vomiting. He was prescribed ondansetron 4 mg to take with the ibuprofen. If he takes the combination, his headache resolves in about an hour.

In recent years, two new classes of acute migraine medications were released (Table 10.9). Gepants are small-molecule calcitonin gene-related peptide (CGRP) receptor antagonists available in oral tablets, while a ditan is a 5HT1F antagonist. The gepants and ditan do not constrict the coronary or cerebral vessels and offer an alternative for those who cannot take the triptans due to cardiovascular concerns. To date, no pediatric safety data is available for either. While there are no pediatric studies or guidelines available to guide the use of gepants or ditans in the treatment of pediatric headache or migraine, many pediatric headache specialists will consider their use, especially in older adolescents, if triptans are not tolerated or contraindicated for certain reasons such as cardiovascular concerns.

Summary for Acute Treatment for Pediatric Headache

When treating acute headache, it is important to devise a treatment plan from the beginning so that patients and their families are prepared when a headache occurs. In general, the recommendations are to treat early into an attack, albeit this may not be as crucial for tension-type headaches; treat with the appropriate medication and dosage; and consider a combination approach as this tends to be more effective. When creating a treatment plan, analgesics are frequently used first in pediatric headache, including migraine, and often are all that are needed, at least initially. Nausea and vomiting should be treated with an antiemetic; antiemetics may also be relevant even when nausea and vomiting are not present as these too can be considered first line in the treatment of migraine. Additionally, triptans are generally safe

in children and can be used alone or in combination with the most support for pairing with nonsteroidal anti-inflammatory drugs. When necessary, a combination of an analgesic, an antiemetic, and a triptan can be administered together. Newer therapies including gepants and ditan show promise but do not have pediatric studies to date.

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Part V
Conclusions

Chapter 11
Transitioning from Pediatric to Adulthood with Regard to Headaches and Their Subsequent Care

Lauren Doyle Strauss and James K. Murtha

Patient Case

Katie is a 17-year-old girl who presents unaccompanied to her pediatrician for headaches that began about 9 months ago. The frequency was initially about 2 episodes per month; however, it has progressively increased and is now about 6 episodes per month. The duration is between 4 hours and a full day. The pain is centered in the frontotemporal region, and it can occur on either side but is almost always unilateral. Its quality is pulsating. The intensity is 6 to 9 out of 10. It is worsened by physical activity and relieved by lying down. It is accompanied by nausea and heightened sensitivity to light and sound. She also reports that she sees zigzag lines in her vision during at least part of the majority of her headache episodes. Although she finds temporary relief from taking acetaminophen, ibuprofen, or an acetaminophen-aspirin-caffeine combination, these seldom bring about complete resolution of the headache. She has no notable past medical history, and the only daily medication that she takes is a combined hormonal contraceptive. She does not smoke cigarettes, drink alcohol, or use illicit drugs.

Introduction

Children and adults have distinct characteristics and patient care needs, both generally and related to specific disease processes. This is why in neurology, providers receive specialized training to care for one population or the other. There is no single time point

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at which a patient transitions from having pediatric characteristics and care needs to those of an adult. The shift is gradual, and there is a considerable period of time during which a patient exhibits an overlap of the features traditionally attributed to each population. To a large degree, the shift begins at a time when patients are still in the care of their childhood healthcare providers. This is certainly the case for patients who suffer from headache disorders. For this reason, it is valuable for providers who care for pediatric headache patients to understand the special considerations that should be taken in the evaluation and management of headache during the transition into adulthood.

Making the Diagnosis

The fundamental components of taking a headache history in an adult patient are largely the same as in a pediatric patient. Headache onset, frequency, duration, location, quality, and intensity as well as associated symptoms, triggers, and exacerbating and alleviating factors must be elicited. The relative prevalence of headache disorders outside of migraine and tension-type headache, however, is higher in the adult than in the pediatric population. If the basic history is not suggestive of one of these more familiar headache disorders, then more targeted questions should be asked to evaluate for others. The International Classification of Headache Disorders third Edition (ICHD-3), which is the official catalogue of diagnostic criteria for all of the headache disorders created by the International Headache Society, is freely available online and can be used as a guide for this targeted history taking [1]. As an example, a patient with unilateral headache not resembling migraine (refer to Table 11.1) should be queried about autonomic symptoms—conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, sweating, miosis, and ptosis—on the side of the face ipsilateral to the pain. The presence of any combination of these would suggest one of the trigeminal autonomic cephalalgias: cluster headache, paroxysmal hemicrania, hemicrania continua, or short-lasting unilateral neuralgiform headache attacks.

Table 11.1 ICHD-3 diagnostic criteria for migraine without aura [1]

A.	At least five attacks fulfilling criteria B–D
B.	Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C.	Headache has at least two of the following four characteristics:
	1. Unilateral location
	2. Pulsating quality
	3. Moderate or severe pain intensity
	4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D.	During headache, at least one of the following:
	1. Nausea and/or vomiting
	2. Photophobia and phonophobia
E.	Not better accounted for by another ICHD-3 diagnosis

The Social History

Another nuance to taking an initial headache history in adult patients involves inquiring about relatively adult-specific habits and activities that may trigger, increase the burden of, or protect against headache attacks. A history taken for any headache patient who currently smokes or has previously smoked should include quantification of his or her smoking in "pack-years," which is the product of the average number of packs smoked per day multiplied by the number of years of smoking. Patients should also be asked about the amount of alcohol and caffeine they consume. As an example of the relevance of this, a study on lifestyle factors in male cluster headache patients found that 78.9% actively smoked, 85.7% consumed alcohol, and 100% drank coffee at the time of referral [2]. All of these rates are considerably higher than those in the general population, suggesting a tendency toward the use of addictive substances in cluster headache sufferers. Smoking is also thought to play a role in the pathogenesis of cluster headache [3]. It is important to know about smoking status in women with migraine because evidence suggests that migraine, smoking, and use of estrogen-containing oral contraceptives may cumulatively increase the risk of ischemic stroke [4] (refer to Section 14.6). Whether alcohol consumption is a trigger should be asked, as this is commonly seen in migraine [5] and cluster headache [6–8]. Headache brought on by sexual activity or orgasm can be a sign of a secondary headache caused by an intracranial pathology or if secondary headaches are ruled out can point toward a diagnosis of "primary headache associated with sexual activity." Patients' employment may have clinical implications. It may expose them to factors that exacerbate their headaches or limit their ability to maintain healthy lifestyle habits. For example, a job may expose the patient to unhealthy food options or excessive caffeine use, require being seated or sedentary, or cause inability to consistently get adequate sleep as may be the case when working the third shift. Patients with restricted licenses such as pilots, truck drivers, or those who operate heavy machinery may have restraints on medication choices.

Painkiller Use

The type and quantity of medication used for acute pain relief must be assessed. Asking about the use of abortive headache medications is essential for adults just as for children, as use of opioids and barbiturates and excessive use of any abortive agent can increase headache burden. Analysis of data from population-based studies has shown that the use of opioids and barbiturates for abortive therapy in patients with episodic migraine was associated with increased risk of transformation to chronic migraine [9, 10]. For this reason, the American Headache Society recommends against the prescription of opioid- or butalbital-containing medications as first-line treatment for headache disorders [11]. It also recommends against frequent

use of abortive medication, suggesting two or fewer doses weekly as a frequency that is unlikely to produce medication-overuse headache. It is important to ask adults about the use of medications for other chronic pain including both prescription opioids and over-the-counter agents, as these can predispose patients to medication-overuse headache. Illicit use of prescription opioids or heroin can have this effect as well.

Drug Seeking

It is important to be able to recognize and respond to behaviors suggestive of drug seeking and abuse of prescribed headache medications in older pediatric and adult patients. These include requests for specific abortive agents, early requests for renewal of prescriptions, and efforts to procure prescriptions from multiple providers. Some suggested responses to concerning behaviors are establishing and documenting expectations for abortive medication use (i.e., a "pain contract"), adopting a policy of prescribing abortive medications in person only and not over the phone, adding a comment on prescriptions requesting that the pharmacist not refill them before a certain date, and performing laboratory drug screening to confirm that medication is being taken or to screen for other drug use. For those patients with multiple prescriptions, the provider may call the pharmacy to obtain an active list and cancel unnecessary or redundant prescriptions. The website for the Centers for Disease Control and Prevention (CDC) contains guidelines for prescribing and directions for using each state's prescription drug monitoring program (PDMP) to determine whether a patient has prescriptions across multiple pharmacies [12].

Contraception

Use of hormonal contraceptives has a number of clinical effects on headache patients. With regard to the evaluation of new headache, oral contraceptive use can increase the risk of cerebral venous thrombosis and reversible cerebral vasoconstriction syndrome, both dangerous causes of secondary headache. It can also worsen headache burden for people with preexisting headache disorders. One study showed that worsening or new onset of migraine after initiation of oral contraceptive use is more likely to occur in migraine with aura than in migraine without aura [13]. For this reason, a female migraineur who reports worsening should be asked if she recently initiated or changed hormonal contraception. In women with migraine, as previously mentioned, there is data supporting a relationship between hormonal contraceptive use and stroke risk. A systematic review of studies on the topic found that odds ratios for ischemic or hemorrhagic stroke in women with migraine who used combined

hormonal contraceptives with any dose of estrogen ranged from 2.08 to 16.9 [14]. A meta-analysis investigating the relationship between migraine and major cardiovascular events found significantly increased rates of ischemic stroke in all women with migraine (relative risk 2.08) and even more so in women with migraine who were actively using oral contraceptives (relative risk 7.02) compared to controls [15]. One study found that there was a tenfold increase in the risk of stroke in women with migraine with aura who were actively smoking and using oral contraceptives compared to controls [4]. The effect is thought to be driven by estrogen. Accordingly, the World Health Organization (WHO) and the American College of Obstetrics and Gynecology (ACOG) recommended that estrogen-containing oral contraceptives not be prescribed to women and girls of any age who have migraine with aura. For female patients younger than 35 who have migraine without aura, their benefit when prescribed for a legitimate indication is considered to likely outweigh their risk. The findings also call for advising migraineurs to avoid the combination of smoking and use of estrogen-containing oral contraceptives. Increased frequency of migraine episodes during the pill-free week of the cycle has been observed in users of estrogen-containing oral contraceptives, likely due to estrogen withdrawal being a trigger for migraine. Hormonal contraceptives can also interact with headache medications. High doses of topiramate, a first-line migraine prophylactic agent, are thought to decrease the serum concentration of the estrogen derivatives in oral contraceptives, rendering them less effective. Older female pediatric patients who are taking or interested in starting topiramate should be counseled about this. If for any of these reasons hormonal contraception is determined to be contraindicated and it remains important for the patient to have a reliable means of preventing pregnancy, an intrauterine device (IUD) may be proposed as an alternative. There are available IUD options without estrogen or without hormones altogether.

Pregnancy

Although pregnancy is uncommon among females under the care of pediatric providers, it is important to be aware of the role of pregnancy in headache evaluation and management. If a patient with a known primary headache disorder presents with a severe, persistent, or different headache episode, evaluation for an unexpected pregnancy should be considered. Pregnant women are at increased risk for a number of pathological processes that present with headache as a symptom. If a pregnant patient without an established diagnosis of a primary headache disorder presents with new-onset headache, a careful evaluation for signs and symptoms of the cause of a secondary headache should be performed (refer to Table 11.2). There are important restrictions for head imaging in pregnant patients, as neither the iodine contrast used for CT nor the gadolinium contrast used for MRI should be administered to a pregnant patient due to potential teratogenicity [16]. Furthermore, even

Table 11.2 Secondary headache etiologies to consider during pregnancy [16]

Secondary headache disorder	In addition to headache, other possible maternal signs/symptoms
Preeclampsia and eclampsia	Preeclampsia • New-onset hypertension • Proteinuria Severe preeclampsia • Hypertension over 160/110 • Oliguria • Liver function abnormalities • Visual disturbance • Thrombocytopenia • Pulmonary edema • Fetal growth restriction Eclampsia • Seizures • Coma
Idiopathic intracranial hypertension	• Visual disturbances (diplopia, transient visual obscurations, blindness) • Papilledema
Subarachnoid hemorrhage	• Thunderclap headache • Blurred vision • Nausea/vomiting • Stiff neck • Syncope • Seizures
Symptomatic tumor	• Cognitive difficulties • Nausea/vomiting • Visual disturbances • Seizures
Pituitary apoplexy	• Thunderclap headache • Visual field defects • Ophthalmoplegia • Nausea/vomiting • Altered level of consciousness/coma
Cerebral venous thrombosis	Cortical vein thrombosis • Seizures Dural venous thrombosis • Papilledema • Seizures • Focal neurologic deficits Deep venous sinus thrombosis • Alteration of consciousness
Reversible cerebral vasoconstriction syndrome	• Recurrent thunderclap headache • Transient focal neurologic deficits • Hypertension with headache • Seizures

CT without contrast should be avoided because it exposes the developing fetus to radiation. MRI without contrast is considered safe, and MR angiography and venography both have diagnostic value when done without contrast. There is no contraindication to lumbar puncture.

A pediatric patient of potential childbearing age should be invited to discuss family planning and contraception strategy and counseled about teratogenic risks of headache medications. The provider and patient should establish a contingency plan for medication changes that is to be enacted for in the case that the patient finds out she is pregnant. If the patient is pursuing pregnancy, then the provider should guide her in making any adjustments to the headache treatment plan that can be made to minimize fetal risk while also optimizing headache control. The treatment plan that will be used during pregnancy should begin *before* pregnancy whenever possible.

It is well documented that a high proportion of pregnant migraineurs experience spontaneous improvement in migraine during pregnancy, especially following the first trimester, with the majority of studies showing improvement in 60–80% of patients [17]. It is helpful to reassure the patient and plan medication use with this in mind. In light of this, some patients will decide to not use a daily preventive medication during pregnancy. Nonetheless, many patients with migraine and other primary headache disorders will continue to experience headaches and require treatment during pregnancy. While nonpharmacologic management strategies including relaxation training, cognitive behavioral therapy, biofeedback, and stress management training are important to consider for any headache patient, their relative role increases in pregnancy due to the limitation of pharmacologic options. The same is the case for procedural therapies, with physical therapy, acupuncture, and nerve blocks being considered both effective and generally safe.

Providers must exercise care in the selection of therapy for headache patients who may become pregnant. Many medications used to treat headache are associated with an increased risk of potential harm to a developing fetus with several highlighted in Table 11.3. Abortive agents that have been studied for use in migraine and are relatively safe include oral acetaminophen, cyproheptadine, and metoclopramide. Cyproheptadine, riboflavin, memantine, pyridoxine, and coenzyme Q10 can be considered as prophylactic options with their lower reported risks. It should be noted that for most of the medications identified as "contraindicated," the reason for this is the *possibility* of risk in the setting of insufficient clinical data to draw definitive conclusions on safety.

Therefore, decisions regarding whether to discontinue a previously effective agent due to pregnancy should be made on a case-by-case basis for most medications, and continuation can be considered if benefit is felt to be considerable and likelihood of comparable benefit from agents with better safety profiles is felt to be low. Given the sensitivity of potential risks, it is advisable to document conversations regarding risk and benefit ratios of medications and treatments.

Table 11.3 Potential teratogenic risks of medications commonly used in the treatment of headache disorders

Medication	Potential teratogenic effect
ACE inhibitors, ARBs	Impaired fetal renal function, fetal lung hypoplasia, skeletal malformation, oligohydramnios, miscarriage
Aspirin	Alteration of maternal and fetal homeostasis, increased perinatal mortality, intrauterine growth restriction, pulmonary hypertension, premature closure of patent ductus arteriosus (PDA)
Beta-blockers	Congenital heart defects, cleft lip/palate, neural tube defects *If near delivery:* fetal bradycardia, respiratory depression, hypoglycemia
Butalbital	Congenital heart defects
Chlorpromazine and promethazine	Third trimester: neonatal extrapyramidal and/or withdrawal symptoms
Ergots	Fetal abnormalities
Magnesium	Low calcium and bone change
NSAIDs	First trimester: miscarriage; third trimester: cleft palate, cardiovascular abnormalities (premature PDA closure)
Opioids	*Higher doses:* fetal adverse effects including physical dependence and withdrawal, retardation of growth, and neonatal respiratory depression *Prolonged use:* physical dependence and postpartum withdrawal
Ondansetron	Congenital heart defects, cleft lip/palate
Topiramate	Cleft lip/palate, structural, intrauterine growth restriction due to metabolic acidosis
Triptans	Possible risk of postpartum hemorrhage and spontaneous abortions
Valproate	Neural tube defects, impaired cognitive development including possible autism

Lactation

The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for the first 6 months and continued breastfeeding with supplementary foods for >1 year with the World Health Organization (WHO) recommending to continue for longer for >2 years. Similar to pregnancy, there needs to be a careful discussion regarding medication effects and safety during lactation, and there are safe options and medication dosing strategies that can allow a mother to safely breastfeed while treating headaches.

Most medications pass into the breastmilk, but this varies with the infant's age, type of medication, and type of administration. Children older than 7 months have similar clearance to adults. There is an increased risk of toxicity in preterm infants (less than 37 weeks' gestation) and infants younger than 1 month. Providers and patients can utilize the helpful and free resource known as the National Library of Medicine's Drugs and Lactation Database (LactMed), which is a peer-reviewed database updated monthly as part of the TOXNET system. It is accessible on a website or through a smartphone application.

For abortive medications, consider advising the "pump and dump" strategy in which breastmilk is pumped for the hours following medication administration to coordinate with an expected medication half-life. Continuing to pump allows for milk supply to be maintained. Acetaminophen and ibuprofen are considered the safest options. The AAP has rated sumatriptan as "safe" due to low oral bioavailability and milk concentrations. Medications to be used with caution are zolmitriptan, which has notably higher bioavailability and CNS penetration, and milk transfer has not been well studied. Dihydroergotamine and ergots can have effects on lactation with reduced milk production.

There is not much known about the effects of nursing on causing or preventing headaches. For patients who had improvement of headaches during pregnancy, there is little guidance on when to initiate preventive medications. The good news is that many preventive medication options have much lower risk than during pregnancy.

Intimate-Partner Violence

Similar to the well-documented association between childhood maltreatment and migraine [18, 19], studies have also shown that there is a higher prevalence of migraine in women who have been victims of physical or sexual intimate partner violence than in the general population [20, 21]. Patients presenting with headache as they near adulthood should therefore be screened for abuse by romantic partners. This can provide a critical opportunity for intervention that may prevent or reduce further victimization. If a patient is accompanied by a partner, family members, or other companions, this screening should be done in private. A possible strategy for this is to make the examination portion private and ask during that time.

Life Impact

The effect of the patient's headache disorder on his or her life should be assessed in the history because it shapes treatment goals and serves as a baseline for measuring progress. The Migraine Disability Assessment Test (MIDAS) is a convenient tool that facilitates quantification of the negative impact of migraine [22] (refer to Table 11.4). It addresses work, home maintenance, caregiving, and social engagement. It can be applied to adults as well as older pediatric patients and can be extrapolated to other headache disorders.

Table 11.4 The Migraine Disability Assessment Test (MIDAS) [22]

1. On how many days in the last 3 months did you miss work or school because of your headaches?
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)
3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?

MIDAS grade	Definition	MIDAS score
I	Little or no disability	0–5
II	Mild disability	6–10
III	Moderate disability	11–20
IV	Severe disability	21+

Transition from Pediatric to Adult Care

The transition from pediatric to adult care is an important undertaking that is inherently involved in the management of headache in patients who are in the care of pediatricians as they become adults. The transition is not merely a transition from one provider to another but a transition in models of care, from the pediatric model in which parents have primary responsibility for the patient's healthcare decisions to the adult model in which the patient has full responsibility. The Child Neurology Foundation (CNF) has created a policy that provides a stepwise guide on the transition from pediatric neurology care to adult neurology care [23, 24]. Many of the concepts can be generalized to apply to transition from pediatric to adult care for neurologic problems, even if the care is not delivered by neurologists. The policy recommends initiating conversation about transition between the ages of 12 and 14. The objective is to be transparent with the patient and family on the plan including the timing or age that the transition will occur and who the transfer of care would be to. In patients with more than mild intellectual disabilities, the continued role of the parents in the adult care of the patient can be planned.

The teenage years should be spent fostering and serially assessing the patient's self-management skills, in this case particularly as they apply to the management of his or her headaches. Providers should establish that the adolescent patient will be expected to have increased personal responsibility, which includes reporting progress at visits, tracking headaches, being the decision maker on abortive medication

use, and ensuring daily preventive medication compliance. The patient's self-motivation in maintaining lifestyle habits that minimize headache burden can also be discussed such as avoiding skipping meals, adequate hydration, avoiding caffeine overuse, and regular consistent sleep schedules. If medication compliance is a concern, a patient can be encouraged to set reminders on their smartphone, create a routine, or use weekly pillboxes. Parents and guardians should be encouraged to support their child in this role and restrain from resuming management. It may be helpful for portions of the visit or entire clinic visits be performed without parents or guardians present. For any patient under age 18, consent for treatment will need to be obtained.

The patient's pertinent medical records, including a summary of prior past medications and diagnostic testing performed, should be prepared and delivered to the adult provider that has been identified to assume care. The pediatric provider should ensure that there is no interruption in care and that adequate medication refills are available as the patient awaits the initial visit with the adult provider. The patient and family should be made aware of the transition from using the pediatric emergency department to the adult one for headache attacks that require such care.

Referral to Neurology

The pediatric-to-adult transition serves as an opportunity for referral of an established headache patient to a neurologist if appropriate in lieu of transfer of responsibility to an adult primary care provider. Straightforward, therapy-responsive cases of most primary headache disorders can be managed by primary care providers. The Spanish Society of Neurology's Headache Study Group has created guidelines for when to refer patients to neurologists and headache subspecialists (refer to Table 11.5). For new-onset headache in which there is difficulty establishing the diagnosis and concern for secondary headache, referral to either a neurologist or a headache subspecialist is advised.

Table 11.5 Indications for neurology referral for migraine and tension-type headache proposed by the Spanish Society of Neurology's Headache Study Group [25]

Headache disorder	Neurology referral	Headache referral
Migraine	• High-frequency episodic migraine • Prolonged attacks • Habitual drugs contraindicated	• Chronic migraine • Frequent and/or atypical auras
Tension-type headache	• Chronic tension-type headache and co-presence of painkiller abuse and/or failed prevention	• None

Moving Out of the Childhood Home

A transition to a more independent living situation occurs for most individuals as they enter adulthood. This often occurs as they start college. In addition to orchestrating the transition to adult care for headache, the pediatric provider can help prepare the patient for successful headache management after leaving the childhood home. In addition to maximizing quality of life for the patient, this reduces parental anxiety. A clear action plan for the management of acute headache attacks should be established. The American Headache Society's Emergency Department, Inpatient, and Refractory Special Interest Section created the Migraine Action Plan (MAP), a suggested treatment plan for home and the emergency room that can be tailored to the patient [26]. The location where the patient will seek further urgent headache care should be determined in advance with options including the student health center, urgent care facility, or emergency department. The patient's new living environment can be equipped to be supportive for the patient during a severe headache. As an example, a dormitory for a migraine patient might have blackout curtains or an eyeshade, polarized computer screen covers to reduce light, noise-cancelling earmuffs, a refrigerator with ice packs, or cool beverages on hand. Additionally, for college-bound patients who have had 504 plan accommodations in place for migraine, what is possible in the college setting should be discussed. College students are no longer covered under the Individuals with Disabilities Education Act (IDEA) of 2004, which focuses on children in public education through high school. There are, however, protections in the Americans with Disabilities Act of 1990 (ADA) and Section 504 of the Workforce Investment Act (WIA) that protect against discrimination for individuals with diagnoses and severity that meet the criteria for disability. When preparing to start college, the student needs to be proactive and contact the institution to report disability or need for accommodations rather than waiting for the institution to identify the need. Section 504 contains expectations of a "reasonable accommodation" in which the student is able to complete an assignment or test without changing the meaning of the score or altering the learning standards.

Return to Patient Case

Katie's headache meets all of the diagnostic criteria for episodic migraine with aura. The first important item to address is the fact that she is on an estrogen-containing oral contraceptive, which can potentially increase the risk of stroke in women who have migraine with aura. The risk-benefit ratio needs to be discussed, and although the patient does not smoke, the additional risk of smoking needs to be advised. She is amenable to discontinuation of OCPs, and when alternative contraception methods are proposed, she expresses that she is actually interested in remaining off contraception altogether. She explains that she is nearing her high school graduation and does not have plans for further education, and that her boyfriend, who is 20, has a stable job as a restaurant manager. In light of these circumstances, the couple is open to having a child. Nonpharmacologic and pharmacologic therapy options are presented to the patient. She expresses an interest in relaxation training, and

resources for this are provided to her. The decision is also made to initiate new abortive and prophylactic medications, with metoclopramide being chosen as the abortive and cyproheptadine being chosen as the prophylactic. Katie is told that she may also continue taking acetaminophen for acute relief, limiting it to no more than 2 doses in a week. She is advised to discontinue the use of ibuprofen and acetaminophen-aspirin-caffeine because both potentially pose risk to a fetus. Katie is asked for her thoughts on transitioning to an adult primary care provider. She says that she anticipates doing this either when she becomes pregnant or in the months following her 18th birthday. She is encouraged to begin the process of identifying a clinic and provider with whom she would like to establish so that her records can be shared in advance of when she like to have her care transferred. Finally, she is asked whether she feels safe at home and in her romantic relationship. She affirms that she does.

The case highlights the following key points from this chapter:

- Estrogen-containing oral contraceptives increase the risk of stroke in women of any age who have migraine with aura.
- Assessment for plans for pregnancy or risk of unexpected pregnancy should be performed regularly with adolescents and young adults. Contraception strategy should be discussed. Medications that possibly can have teratogenic effects should be reviewed.
- If a patient is planning pregnancy, then the plan for treatment of headache should be discussed and implemented prior to pregnancy.
- Nonpharmacologic approaches are the mainstay of headache management during pregnancy and lactation. Medication choices can be affected; however, there are still options that are demonstrated to be both safe and effective.
- Older pediatric patients presenting for initial evaluation of headache should be screened for intimate partner violence in addition to maltreatment by adults.
- Plans for transfer of care for headache from the pediatric provider to an adult provider should be continuously and transparently addressed.

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Chapter 12
Future of Pediatric Headache: Where Do We Go from Here?

Lauren Doyle Strauss and James K. Murtha

Patient Case
Garrett is a 16-year-old boy who has struggled for years with refractory headaches diagnosed as chronic migraine. His mother and father both come to the visit and express their frustration that he has only had minimal relief despite trying multiple prophylactic and abortive medication options. They have seen several new treatments for adults advertised and are interested in learning more about them and whether they could be a possible treatment option for Garrett.

Introduction

In the past, many therapies for headache, especially migraine, have been borrowed from other areas of medicine (e.g., treatments for blood pressure, mood, and seizures). In recent years, there has been great excitement about the release of new headache medications and treatments developed and studied specifically for migraine and other headache disorders. These therapies may also have benefit and safety in children; however, many are not currently approved by the Food and Drug Administration (FDA) due to insufficient data in this population. Clinicians would like to expand their options offered to patients but are faced with the need to balance this with limited information on safety and effectiveness. If a clinician chooses to prescribe one of these treatments for

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children, there are additional barriers to reimbursement for off-label therapies, which increases cost to the patient. More high-quality research on these pharmacologic and device-mediated therapies is needed in the pediatric population to explore safety and support FDA approval, which will hopefully improve coverage and access.

Onabotulinum Toxin A

Onabotulinum toxin A was approved for chronic migraine prophylaxis in adults in 2010 after the PREEMPT trials demonstrated that its use was associated with a significantly greater decrease in the frequency of headache days compared to placebo [1]. The published evidence concerning its use for pediatric migraine and chronic daily headache, while promising, is less robust as it is limited to retrospective analyses. In three small retrospective studies (one with 12 patients aged 14–18 years [2], one with 10 patients aged 11–17 years [3], and one with 10 patients aged 13–17 [4]), a considerable portion of the patients experienced improvement in headache frequency, and the treatment was found to be generally well tolerated. A review of 45 patients in 2012 showed a statistically significant decrease in monthly headache days from 27.4 to 22.2 after a single injection [5]. A 2018 review of 10 patients treated for variable durations during a 5-year period showed significant decreases in headache frequency, duration, and intensity from pretreatment to posttreatment [6]. An unpublished 2017 randomized placebo-controlled trial sponsored by the manufacturer of a particular brand of onabotulinum toxin A showed no difference in reduction in headache days after 12 weeks between a 155-unit treatment arm (−6.3 days' change from baseline), a 74-unit treatment arm (−6.4 days), and the placebo arm (−6.8 days) [7]. In summary, the available evidence to date is mixed. There has been a randomized, double-blind, placebo-controlled crossover study in progress with completion expected in 2020 [8].

Despite the lack of FDA approval for use in children, it is reasonable to consider onabotulinum toxin A for chronic migraine in adolescents based on their theoretical similarity to adults. In the standard protocol for treatment of adults, a total dose of 155 units is administered via intramuscular injection across 31 sites on the head and neck every 12 weeks. Onabotulinum toxin A and other botulin toxins are used in other pediatric conditions. In 2019, the FDA approved onabotulinum toxin A use for upper limb spasticity for children 2–17 years with dosing not to exceed 8 units/kg of body weight or 300 units total. In clinical practice, insurers reserve coverage for refractory chronic migraine in adults, meaning that a patient must have failed trials of two other prophylactic agents at therapeutic doses, but pediatric patients have different coverage policies.

Anti-CGRP Monoclonal Antibodies

The anti-calcitonin gene-related peptide (CGRP) receptor monoclonal antibodies constitute the first class of medications specifically designed for the prophylactic treatment of headache. Erenumab, fremanezumab, and galcanezumab received FDA approval for the treatment of episodic and chronic migraine in 2018, with galcanezumab also being approved for the treatment of cluster headache. All are administered via subcutaneous injection, with erenumab and galcanezumab administered at 1-month intervals and fremanezumab at either 1- or 3-month intervals. Adverse effects in the clinical trials were few and mild; however, long-term safety remains to be seen and effects on fertility and fetal development have not been investigated. With regard to the pediatric population, a phase I study for erenumab is currently being conducted by its manufacturer [9]. Phase III trials evaluating its use for pediatric episodic and chronic migraine are also recently underway [10, 11]. A 2018 perspective paper by pediatric headache specialists advocated for consideration of anti-CGRP monoclonal antibodies in carefully selected pediatric patients with migraine, new daily persistent headache, chronic post-traumatic headache with migrainous phenotype, and cluster headache [12].

Similar to the anti-CGRP monoclonal antibodies for prophylactic care for headache patients, there has also been a few new classes of acute migraine medications developed (discussed previously in Chap. 10). Gepants, which are small-molecule calcitonin gene-related peptide (CGRP) receptor antagonists, as well as a ditan, which is similar yet different to triptans as it is a 5-HT 1F serotonin receptor antagonist, have been approved for adult use as an acute headache treatment. As with the anti-CGRP monoclonal antibodies, further investigation with clinical trials and studies is needed to better establish their use and effectiveness in the pediatric population.

Neuromodulation

Neuromodulation, a therapeutic modality for neurologic pathology characterized by the delivery of electrical or magnetic stimuli to the brain or nerves, is available for both prophylactic and abortive headache treatment in adults. It can be used as an adjunct to pharmacotherapy or even an alternative in patients who are particularly medication averse. While efficacy data is generally mixed, several noninvasive neuromodulation devices have FDA approval for the treatment of headache disorders in adolescents and adults due in large part to favorable safety profiles [13]. Noninvasive vagal nerve stimulation (nVNS) has FDA approval for abortive and preventative treatment of migraine in patients over 12 years of age and abortive treatment of episodic cluster headache attacks in adults [13–16]. Electrical trigeminal nerve

stimulation (eTNS) has approval for both abortive and prophylactic treatment of migraine in adults but not in the pediatric population [17, 18]. Despite not having approval in pediatrics, eTNS is used in this population off-label [19]. Single-pulse transcranial magnetic stimulatioin (sTMS) has approval for both abortive and prophylactic treatment of migraine in adults and adolescents 12 year of age and older [20, 21]. Additionally, remote electrical neuromodulation (REN) has been approved as an abortive treatment for episodic or chronic migraine patients with or without aura 12 years of age and older [22]. There are several other neuromodulation strategies that are more invasive and may be recommended by headache subspecialists for adult patients with refractory cluster headache, migraine, or other headache types but these will not be reviewed as they are beyond the scope of this text.

Overall, while there is minimal data on neuromodulation for headache in the pediatric population, several of these neurmodulation devices have garnered approval in the adolescent population as noted above. Even without approval (namely eTNS), neuromodulation has been used as referenced above. This, along with the safety profiles and low side effect potential makes neuromodulation a plausible treatment option for many patients with various types of pediatric headahce. This is especially true when patients or their families are looking to avoid medications and possible side effects, as often is the case when evaluating and treating a pediatic headache patient.

Return to Patient Case

Garrett has kept a headache journal for the last 6 months and has averaged about 20 headache days per month with his typical migraine episode occurring on 75% of these days. He therefore has chronic migraine and would meet the adult indication criteria for onabotulinum toxin A. At age 16, he is physiologically similar to an adult, and botulinum toxins are used in pediatric patients for other conditions without significant safety concerns. In light of these facts, he is deemed an appropriate candidate for onabotulinum toxin A. An anti-CGRP monoclonal antibody is considered; however, given the absence of safety data for children, it is considered a less prudent choice. Treatment with onabotulinum toxin A is initiated. sTMS is discussed with Garrett and his parents as a potential adjunctive therapy that could be introduced if his headache burden remains problematic in the future.

The case highlights the following key points from this chapter:

- Onabotulinum toxin A has mixed data for efficacy in pediatric headache and does not currently have FDA approval. It is used in other pediatric conditions and may be considered in adolescents with refractory migraine and chronic daily headache.
- Anti-CGRP receptor monoclonal antibodies have promise for use in pediatric migraine and potentially cluster headache based on their demonstrated efficacy in adults. Investigation of safety and efficacy in the pediatric population is in its early stages; however, the use of agents in this class can be considered in carefully selected patients.
- Neuromodulation has mixed data as headache therapy for adults and may function best as an adjunct to medical therapy. It is FDA approved for this largely due

to its favorable safety profile, and it is reasonable to expect that it will become an option for children for the same reason.

Conclusion

It is an exciting time in the world of headache medicine, especially in pediatric headache medicine. While in the past, most, if not all, prophylactic treatments were stumbled upon as they were originally created for a different medical concern and found to be beneficial with treating headaches, more recently there have been numerous advancements that have been conceptualized, created, studied, and brought to market specifically for the treatment of headache. While these treatments may further the care for pediatric headache patients, much work is still left to be done to make this happen for our patients. The future of pediatric headache is here, as laid above, with new, novel, and specifically targeted treatments, but further investigation and studies are needed in the coming years to gain approval and acceptance for their utilization in pediatric headache akin to that which is being currently seen with our adult headache population.

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