Pediatric Migraine

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KEYWORDS

• Migraine • Headache • Children • Adolescents

Migraine is a chronic, progressive, and debilitating disorder that has an impact on the lives of millions of individuals. The origins of the disability can be traced into childhood and adolescence for most adult migraine sufferers.[1] Accurate diagnosis and aggressive treatment interventions during childhood and adolescence are essential to prevent the decades of suffering and diminished quality of life that are directly attributable to migraine. Adequately addressing migraine during adolescence has as much importance on the patient's overall well-being as providing immunizations and weight management.

Diagnosing migraine in children can be a particular challenge. The clinical manifestations of migraine vary widely through childhood because the disorder may be expressed differently or incompletely. Mimickers of migraine also emerge during childhood to complicate the diagnostic landscape. Such entities as mitochondrial or metabolic disorders, epilepsy syndromes, vascular disorders, and congenital malformations may present with episodic symptoms, including headache. In addition, the medical history can be limited by the child's inability to articulate the symptoms, coupled with parental interpretation, distortion, and editorial. Furthermore, children are often brought for medical evaluation at the onset of transient neurologic, autonomic, gastrointestinal, or visual symptoms, before the characteristic recurrent pattern is established, and, curiously, headache may not be the primary symptom. The key aspect to recognizing the spectrum of migraine in children is to appreciate that migraine is an episodic disorder separated by symptom-free intervals.

The purpose of this article is to review the clinical manifestations and management options for migraine in children and adolescents, with an emphasis on those entities peculiar to young children. All pharmacologic comment is ''off-label.''

EPIDEMIOLOGY

Headaches are common during childhood. Bille's landmark epidemiologic survey conducted in the 1950s in Sweden of 6000 school children found that the prevalence of generic ''headache'' ranged from 37% to 51% in 7-year-old children and gradually

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rose to 57% to 82% by adolescence.[2] Frequent or recurring patterns of headache, of which migraine represents a significant subset, occurred in 2.5% of 7-year-olds and in up to 15% of 15-year-olds.

Subsequent epidemiologic studies have found that the prevalence of migraine headache steadily increases through childhood, peaking in adolescence. Depending on the diagnostic criteria used, the prevalence increases from 3% in the preschool years, to 4% to 11% by the elementary school years, and then up to 8% to 23% during the high school years. Before puberty, boys have more headaches than girls, but after puberty, migraine headaches occur more frequently in girls.[3–5]

The incidence of migraine peaks earlier in boys than in girls.[6] The mean age of onset of migraine is 7 years for boys and 11 years for girls; the gender ratio also shifts during the adolescent years (**Table 1**). The incidence of migraine with aura peaks earlier than the incidence of migraine without aura.[5–13]

Classification of Pediatric Migraine

The International Classification of Headache Disorders for migraine is shown in **Box 1** and is available on-line ([14]).

There are three primary groups:

1. Migraine without aura (formerly common migraine)
2. Migraine with aura (formerly classic migraine)
3. Childhood ''periodic syndromes'' that are commonly precursors of migraine

Notably absent in the 2004 classification system are several clinical entities peculiar to childhood, such as ''Alice in Wonderland'' syndrome, benign paroxysmal torticollis, confusional migraine, and ophthalmoplegic migraine (OM), which are discussed for completeness.

MIGRAINE WITHOUT AURA

This is the most frequent form of migraine in children and adolescents (60%–85% of cases). The diagnostic criteria are shown in **Box 2** and include three modifications to increase sensitivity of diagnosis for children: brief duration (1–72 hours), bilateral or bifrontal location (age <15 years), and the inference of photophobia and phonophobia by behavioral response rather than verbal report.

The key feature of migraine with aura in children is episodes of intense disabling headache separated by symptom-free intervals. The criteria require at least five distinct attacks lasting 1 to 72 hours and permit attacks to be briefer than in adults (range: 4–72 hours). The location of the pain may be unilateral or, in children younger than 15 years of age, bilateral (bifrontal or bitemporal). The quality of pain is typically pulsing or throbbing, a symptom that may require specific questioning in young children. By definition, the pain is moderate to intense and aggravated by routine physical activity, such as walking or climbing stairs. The accompanying associated autonomic

Table 1
Prevalence of migraine headache through childhood

	Age		
	3–7 Years	7–11 Years	15 Years
Prevalence	1.2%–3.2%	4%–11%	8%–23%
Gender ratio	Boys > girls	Boys = girls	Girls > boys

Box 1
Migraine classification

Migraine without aura
Migraine with aura
Typical aura with migraine headache
Typical aura with nonmigraine headache
Typical aura without headache
Familial hemiplegic migraine
Sporadic hemiplegic migraine
Basilar-type migraine
Childhood periodic syndromes that are commonly precursors of migraine
Cyclic vomiting
Abdominal migraine
Benign paroxysmal vertigo of childhood
Retinal migraine
Complications of migraine
Chronic migraine
Status migraine
Persistent aura without infarction
Migrainous infarction
Probable migraine

Box 2
Diagnostic criteria for pediatric migraine without aura

A. At least five attacks fulfilling criteria B through D

B. Headache attacks lasting 1 to 72 hours

C. Headache has at least two of the following characteristics:

1. Unilateral location, which may be bilateral or frontotemporal (not occipital)
2. Pulsing quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (eg, walking, climbing stairs)

D. During the headache, at least one of the following:

1. Nausea or vomiting
2. Photophobia and phonophobia, which may be inferred from a child's behavior

E. Not attributed to another disorder

features (nausea, vomiting, photophobia, and phonophobia) may be as disabling as the pain. The latter two features may be inferred by the patient's behavior if the child withdraws to a quiet dark place during the attack. The International Headache Society (IHS) criteria wisely also state that the headache must "not attributed to another disorder," implying that the prudent physician should carefully consider other possible causes for the recurrent headaches.

MIGRAINE WITH AURA

The disorders within the migraine with aura spectrum reflect the concept that the focal symptoms, such as visual disruptions, hemiparesis, and aphasia, are manifestations of the regional neuronal depolarization and oligemia caused by cortical spreading depression (CSD). Clinical entities of childhood with focal neurologic symptoms, previously termed *migraine variants*, such as hemiplegic and basilar type, now are included within this category of migraine with aura.

Approximately 15% to 30% of children and adolescents who have migraine report visual disturbances, distortions, or obscurations before, or as, the headache begins. The visual symptoms begin gradually and last for several minutes (typical aura). The most frequent forms are binocular visual impairment with scotoma (77%), distortion or hallucinations (16%), and monocular visual impairment or scotoma (7%).[15] Formed illusions (eg, spots, balloons, colors, rainbows) or other bizarre visual distortions (eg, Alice in Wonderland syndrome) may be described, albeit infrequently.

Sudden images and complicated visual perceptions should prompt consideration of benign occipital epilepsy, specifically Panayiotopoulos syndrome.[16] Transient visual obscurations may also be described with idiopathic intracranial hypertension; thus, not all visual symptoms with headache are attributable to migraine with aura.

BASILAR-TYPE MIGRAINE

Basilar-type migraine (BM) represents 3% to 19% of childhood migraine and has a mean age onset of 7 years. Attacks are characterized by episodes of dizziness, vertigo, visual disturbances, ataxia, or diplopia as the aura, followed by the headache phase. The pain of BM may be occipital in location, unlike the usual frontal or bitemporal pain of typical migraine. The diagnostic criteria require two or more symptoms and emphasize bulbar and bilateral sensorimotor features (**Box 3**). Familiar forms of BM linked to the same genes as familial hemiplegic migraine (FHM), types 1 and 2, have recently been reported.[17]

FAMILIAL HEMIPLEGIC MIGRAINE

No form of migraine has yielded more information about the underlying molecular genetics of migraine than FHM. FHM, type 1, is an uncommon autosomal dominant form of migraine with aura caused by a missense mutation in the calcium channel gene (CACNA1A) linked to chromosome 19p13. Clinically, FHM is a migraine headache heralded by an aura that has "stroke-like" qualities, producing some degree of hemiparesis (**Box 4**). The transient episodes of focal neurologic deficits precede the headache phase by 30 to 60 minutes but, occasionally, extend well beyond the headache itself (hours to days). The location of headache is often (but not invariably) contralateral to the focal deficits. Many children and adolescents report transient somatosensory symptoms heralding an attack with focal paresthesias around the mouth and hand (eg, chiro-oral) without weakness; this does not fulfill the criteria for hemiplegic migraine. Genetic testing is commercially available for FHM type 1.

Box 3
Diagnostic criteria for basilar-type migraine

A. Fulfills criteria for migraine with aura

B. Accompanied by two or more of the following types of symptoms:

1. Dysarthria
2. Vertigo
3. Tinnitus
4. Hypacusia
5. Diplopia
6. Visual phenomena in the temporal and nasal fields of both eyes
7. Ataxia
8. Decreased level of consciousness
9. Decreased hearing
10. Double vision
11. Simultaneous bilateral paresthesias

C. At least one of the following:

1. At least one aura symptom develops gradually over 5 minutes or more, and different aura symptoms occur in succession over 5 minutes or more.
2. Each aura symptoms lasts more than 5 minutes and 60 minutes or less.

D. Headache-fulfilling criteria: migraine without aura begins during the aura or follows aura within 60 minutes.

Box 4
Diagnostic criteria for familial hemiplegic migraine

A. Fulfills criteria for migraine with aura

B. Aura consisting of fully reversible motor weakness and at least one of the following:

1. Fully reversible visual symptoms, including positive features (eg, flickering lights, spots, lines) or negative features (eg, loss of vision)
2. Fully reversible sensory symptoms, including positive features (eg, pins and needles)
3. Fully reversible dysphasic speech disturbance

C. At least two of the following:

1. At least one aura symptom develops gradually over more than 5 minutes
2. Aura symptom lasts more than 5 minutes and less than 24 hours
3. Headache that fulfills criteria for migraine without aura begins during the aura or follows the onset of aura within 60 minutes

D. At least one first-degree or second-degree relative has had an attack

E. At least one of the following:

1. History and physical and neurologic examinations not suggesting any organic disorder
2. History or physical or neurologic examination suggesting such a disorder, which is ruled out by appropriate investigations

FHM types 2 and 3 are clinically quite similar but have distinctly different molecular mechanisms: FHM type 2 attributable to point mutation of the α_2-subunit of the sodium-potassium pump (ATP1A2) gene on chromosome 1q21 to 23 and FHM type 3 attributable to sodium channel gene mutation (SCN1A).[18,19]

Sporadic hemiplegic migraine includes those patients who present with the abrupt onset of focal neurologic signs or repetitive episodes of focal neurologic symptoms without a family history.

PERIODIC SYNDROMES OF CHILDHOOD THAT REPRESENT PRECURSORS OF MIGRAINE

The term *migraine variants* was formerly applied to this grouping of migraine precursors and some of the forms of migraine with aura; however, today, they are more appropriately categorized according to IHS criteria. Three childhood conditions are included in the category of periodic syndromes: benign paroxysmal vertigo, cyclic (or cyclical) vomiting syndrome (CVS), and abdominal migraine. A fourth, benign paroxysmal torticollis, is discussed in this section, because recent molecular genetic information has demonstrated linkage to migraine.

Benign paroxysmal vertigo occurs in young children with abrupt episodes of unsteadiness or ataxia. The child may appear startled or frightened by the sudden loss of balance. Witnesses may report nystagmus or pallor. Verbal children may describe dizziness and nausea. The spells may occur in clusters that typically resolve with sleep. In series of patients available for long-term follow-up, many evolve to BM. The diagnosis of benign paroxysmal vertigo is based on a characteristic clinical history, but caution must be exercised to exclude seizure disorders (eg, benign occipital epilepsy), otologic pathologic conditions, posterior fossa lesions, cervical spine abnormalities, or metabolic disorders.

A pattern of cycling episodes of vomiting may be seen with a variety of gastrointestinal, neurologic, and metabolic disorders, but a significant subset of children with stereotyped episodes of vomiting have a migrainous basis for their symptoms, which represent CVS. The key clinical feature of CVS is recurrent episodes of severe vomiting with interval wellness (**Box 5**).

The episodes occur on a regular, often predictable, basis every 2 to 4 weeks, lasting 1 to 2 days, and commencing in the early morning hours. The age of onset is approximately 5 years, and boys and girls are affected equally. The age of diagnosis is approximately 8 years, and most children ''outgrow'' their symptoms by the age of 10 years; however, a significant proportion of patients have symptoms through adolescence and even as young adults.

After a complete diagnostic investigation has excluded other causes of the cyclic vomiting pattern, a comprehensive treatment plan, including acute and prophylactic measures, may be instituted. For acute treatment of attacks, aggressive hydration, sedation, and an antiemetic agent represent the mainstays. Oral or intravenous hydration with a glucose-containing solution is essential. Antiemetic choices include the following:

Ondansetron (0.3–0.4 mg/kg administered intravenously or 4–8 mg administered as an oral disintegrating form or tablet)
Promethazine (0.25–0.5 mg/kg per dose administered intravenously or orally)
Metoclopramide (1–2 mg/kg up to 10 mg twice a day administered intravenously or orally)
Prochlorperazine (2.5–5 mg twice a day administered intravenously)

During an attack, sedation with a benzodiazepine (lorazepam, 0.05–0.1 mg/kg up to 5 mg) or diphenhydramine (0.25–1 mg/kg) is often necessary. Cautious enthusiasm for

Box 5
Diagnostic criteria for cyclic vomiting syndrome

Recurrent episodic attacks, usually stereotypical in the individual patient, of vomiting and intense nausea. Attacks are associated with pallor and lethargy. There is complete resolution of symptoms between attacks.

Diagnostic criteria

A. At least five attacks fulfilling criteria B and C

B. Episodic attacks, stereotypical in the individual patient, of intense nausea and vomiting lasting 1 to 5 days

C. Vomiting during attacks occurs at least five times per hour for at least 1 hour

D. Symptom-free between attacks

E. Not attributed to another disorder and history and physical examination do not show signs of gastrointestinal disease

use of nasal (5 mg) or subcutaneous (~0.07 mg/kg) sumatriptan preparations is growing as field experience mounts, although none of the triptan preparations have been subjected to blind clinical trials for CVS and none are yet approved by the US Food and Drug Administration (FDA).

Initiation of a migraine prophylactic agent for CVS should be strongly considered because CVS is an extraordinarily disabling condition for the child and the family. Options include the following:

Cyproheptadine (2–4 mg/d)
Amitriptyline (5–25 mg/d)
Anticonvulsants
  Valproate (~10–14 mg/kg/d)
  Topiramate (1–10 mg/kg/d)
Beta-blockers (eg, propranolol)
Calcium channel blockers (eg, verapamil).

Abdominal migraine is characterized by episodic vague, midline, or periumbilical abdominal pain (**Box 6**). Abdominal migraine includes a subset of patients with chronic recurrent abdominal pain who have features that overlap with those of migraine without aura. Abdominal migraine generally occurs in school-aged children, who report recurrent attacks of midline or upper abdominal pain that is dull in nature and generally lasts for hours.

As with CVS, the key to this entity is to recognize the recurrent pattern of symptoms and to exclude other gastrointestinal or renal diseases by appropriate investigations. An up-to-date reference list for CVS and abdominal migraine is available on-line ([20]).

Benign paroxysmal torticollis is a rare paroxysmal dyskinesia characterized by attacks of head tilt alone or tilt accompanied by vomiting and ataxia that may last hours to days. Other tortional or dystonic features, including truncal or pelvic posturing, may be seen. Attacks first manifest during infancy between 2 and 8 months of age.

Paroxysmal torticollis is likely an early-onset variant of basilar migraine, but the differential diagnosis must include gastroesophogeal reflux (Sandifer syndrome), idiopathic torsional dystonia, and complex partial seizure. Particular attention must be paid to the posterior fossa and craniocervical junction, however, where congenital or acquired lesions may produce torticollis. Once the diagnosis is established and the benign nature is confirmed, there may be no requirement for treatment beyond reassurance.

Box 6
Diagnostic criteria for abdominal migraine description

An idiopathic recurrent disorder seen mainly in children and characterized by episodic midline abdominal pain manifesting in attacks lasting 1 to 72 hours with normality between episodes. The pain is of moderate to severe intensity and is associated with vasomotor symptoms, nausea, and vomiting.

Diagnostic criteria

A. At least five attacks fulfilling criteria B through D

B. Attacks of abdominal pain lasting 1 to 72 hours

C. Abdominal pain has all the following characteristics:

1. Midline location, periumbilical or poorly localized
2. Dull or "just sore" quality
3. Moderate or severe intensity

D. During abdominal pain, at least two of the following:

1. Anorexia
2. Nausea
3. Vomiting
4. Pallor

E. Not attributed to another disorder; history and physical examination do not show signs of gastrointestinal or renal disease, or such disease has been ruled out by appropriate investigations

OTHER UNUSUAL FORMS OF MIGRAINE IN CHILDHOOD

Alice in Wonderland syndrome represents the spectrum of migraine with aura, but the visual aura is quite atypical and may include bizarre visual illusions and spatial distortions preceding an otherwise nondescript headache. Affected patients describe distorted visual perceptions, such as micropsia, macropsia, metamorphopsia, teleopsia, and macro- or microsomatognopsia. The visual symptoms likely represent CSD and oligemia involving the parieto-occipital region heralding the headache.

Confusional migraine has perceptual distortions as a cardinal feature. Affected patients, usually boys, abruptly become agitated, restless, disoriented, and occasionally combative. The confusion phase may last minutes to hours. Later, once consciousness returns to baseline, the patients describe an inability to communicate, frustration, confusion, and loss of orientation to time, and they may not recall a headache phase at all. Confusional migraine often occurs after seemingly innocuous head injury occurring in sports (eg, soccer, football, skating). Clearly, any sudden unexplained alteration of consciousness after head injury warrants investigation for intracranial hemorrhage, drug intoxication, metabolic derangements, or epilepsy.

Clinically, confusional migraine most likely represents an overlap between hemiplegic migraine and BM. Patients who present with unilateral weakness or language disorders should be classified as having hemiplegic migraine, and patients with vertiginous or ataxic patterns should be classified as having BM.

Ophthalmoplegic migraine (OM) has been removed from the migraine spectrum into the group of ''cranial neuralgias'' as a result of elegant neuroimaging evidence demonstrating an underlying demyelinating-remyelinating mechanism. The key clinical feature

is painful ophthalmoparesis. The pain may be a nondescript ocular or retro-ocular discomfort. Ptosis, limited adduction, and vertical displacement (eg, cranial nerve III) are the most common objective findings. The oculomotor symptoms and signs may appear well into the headache phase rather than heralding the headache, contrary to the sequence of typical migraine. The signs may persist for days or even weeks after the headache has resolved. Because OM is no longer viewed as migraine, eventually, the term *ophthalmoplegic migraine* is likely to evolve to *ophthalmoplegic neuralgia* or *neuralgiform disorder*.

The migraine precursors and these unusual forms of migraine with aura are unique to pediatrics and represent a challenging group of disorders characterized by the abrupt onset of focal neurologic signs and symptoms (eg, hemiparesis, altered consciousness nystagmus, ophthalmoparesis) followed by headache. Frequently, these ominous neurologic signs initially point the clinician in the direction of epileptic, cerebrovascular, traumatic, or metabolic disorders, and the migraine diagnosis become apparent only after thorough neurodiagnostic testing. Some of these entities occur in infants and young children, in whom a history is limited. Only after obtaining a careful history and performing a physical examination and appropriate neurodiagnostic studies can these diagnoses be comfortably entertained. All represent diagnoses of exclusion.

MANAGEMENT

Once the diagnosis of migraine is established, a balanced, flexible, and individually tailored treatment plan can be put in place. It is important to educate the patient and the family about the diagnosis of migraine and to provide reassurance about the absence of other life-threatening disorders. This essential explanation and reassurance can get the family ''on board'' with the treatment regimen; otherwise, all subsequent efforts are likely to be fruitless.

When developing the treatment plan, the first step is to appreciate the degree of disability imposed by the patient's headache. Understanding the impact of the headache on the quality of life can guide the decisions regarding the most appropriate therapeutic course.[21,22]

The fundamental goals of long-term migraine treatment have been established:[23]

1. Reduction of headache frequency, severity, duration, and disability
2. Reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
3. Improvement in the quality of life
4. Avoidance of acute headache medication escalation
5. Education and enablement of patients to manage their disease to enhance personal control of their migraine
6. Reduction of headache-related distress and psychologic symptoms

To achieve these goals, the treatment regimen must balance biobehavioral strategies and pharmacologic measures. Biobehavioral treatments include biofeedback, stress management, sleep hygiene, exercise, and dietary modifications (**Box 7**). The value of these interventions cannot be overstated. Virtually all migraine sufferers can benefit from review of these measures; however, certainly, in patients who have more frequent attacks, even daily migraine, and a greater degree of disability, there is a greater need to reinforce the following measures. Biofeedback and stress management, which are underused therapies, have been subjected to controlled trials and have been reviewed recently.[24]

Box 7
Biobehavioral therapies for pediatric migraine

Identification of migraine triggers
Biobehavioral
Biofeedback
Electromyographic biofeedback
Electroencephalography
Thermal hand warming
Galvanic skin resistance feedback
Relaxation therapy
Progressive muscle relaxation
Autogenic training
Meditation
Passive relaxation
Self-hypnosis
Cognitive therapy/stress management
Cognitive control
Guided imagery
Dietary measures
"Avoidance diets"
Caffeine moderation
Herbs
Butterbur root
Feverfew (*Tanacetum parthenium*)
Ginkgo
Valerian root
Minerals
Magnesium
Vitamins
Riboflavin
Acupuncture
Aroma therapy

The basic recommendations given to migraine sufferers include regular sleep and exercise, moderation of caffeine intake, and adequate hydration. The role of diet remains controversial.[25] Somewhere between 7% and 44% of patients report that a particular food or drink can precipitate a migraine attack.[26,27] In children, the principal dietary triggers are cheese, chocolates, and citrus fruits. Wholesale dietary elimination of a list of foods is, however, not recommended. Elimination diets are excessive and set the stage for a battleground at home when parents attempt to enforce a restrictive diet on an unwilling resistant adolescent. The ensuing family friction may ultimately heightened tensions at home, worsening the headache pattern. A more reasonable approach is to

review the list of foods thought to be linked to migraine and encourage the patient to keep a headache diary to see if a temporal relation exists between ingestion of one or more of those foods and the development of headache. If a link is discovered, common sense dictates avoidance of the offending food substance.

Within **Box 7** are included some of the complementary and alternative treatment measures for pediatric and adult migraine. Few have been subjected to controlled trials in children, but they have become commonly used and recommended on patient education Web sites. Magnesium (~400–800 mg/d) and riboflavin (~400 mg/d) have demonstrated efficacy in controlled prophylaxis trials and are currently recommended for the prevention of migraine in adults.[28] Data regarding other herbal remedies are limited in children. Butterbur root, for example, was compared with placebo and music therapy, and only music therapy showed superiority compared with placebo during the trial period; however, during extended follow-up, music therapy and butterbur root showed value.[29]

An intriguing study was conducted by Hershey and colleagues[30] to explore the value of coenzyme Q10 (CoQ10) in the management of migraine. These researchers measured the levels of CoQ10 in 1550 children and found that 33% had values less than the reference range. These patients were supplemented with CoQ10 at a rate of 1 to 3 mg/kg/d, and in follow-up, their headache frequency improved from 19 (±10) to 12 (±11) per month (P<.001). These investigators proposed that CoQ10 deficiency may be a common phenomenon in children with frequent migraine.[30] This clearly warrants further study.

Overuse of ''over-the-counter'' analgesics (more than five times per week) can be a contributing factor to frequent, even daily, headache patterns. When recognized, patients who are overusing analgesics must be educated to discontinue the practice. Retrospective studies have suggested that this recommendation alone can decrease headache frequency.[31,32]

The pharmacologic management of pediatric migraine has been subjected to thorough review, but controlled data are, unfortunately, limited; therefore, recommendations are all ''off-label.''[33–37]

Acute treatments represent the mainstay of migraine management. The patient should be offered several acute treatment options to explore after the initial office visit so that he or she may determine what works most effectively. Regardless of the acute treatment selected, there are several basic guidelines regarding the use of acute treatments that must be included as part of the patient's educational process. The essential message is to give enough and to give it early.

1. Take the medicine as soon as possible when the headache begins (within 20–30 minutes).
2. Take the appropriate dose; do not ''baby'' the headache.
3. Have the medicine available at the location where the patient usually has his or her headaches (eg, school), and complete the school medicine forms.
4 Avoid analgesic overuse (more than three doses of analgesic per week).

For the acute treatment of migraine, the most rigorously studied agents are ibuprofen, acetaminophen, and selected ''triptans'' (eg, rizatriptan and almotriptan tablets, sumatriptan and zolmitriptan nasal sprays), which have shown safety and efficacy in controlled trials (**Table 2**). Although the triptans have revolutionalized acute migraine treatment for adults, none have been approved by the FDA for use in children and adolescents, even though multiple studies have demonstrated the safety of their use in children.[38,39]

Table 2
Evidence summary for treatment of acute attacks of migraine in children and adolescents

Drug	Class	Study Design	n	Age (Years)	Primary End Point	Efficacy	Placebo Response	Clinical Impression of Effect[a]	Adverse Effects	Reference
NSAIDs and nonopiate analgesics										
Ibuprofen	II	DBPC	88	4–16	HA response	68%	37%	+++	Infrequent	45
	II	DBPC	84	6–12	HA response	76%	53%	+++	Infrequent	46
	II	DBPCCO	32	10–17	HA relief	69%	28%	+++		63
Acetaminophen	II	DBPC	88	4–16	HA response	54%	37%	++	Infrequent	45
Triptans (serotonin$_{1B/1D}$ receptor agonists)										
Nasal spray	II	OL	58	4–11	HA relief	78%	—	++	Occasional to	64
Sumatriptan	III	DBPC	14	6–10	HA response	86%	43%	+++	frequent	41
Zolmitriptan	I	DBPC	510	12–17	2-hour HA response	63%–66%	53%	+++		39
	I	SB-DBPC	171	12–17	1-hour HA response	58%	43%	+++		42
Oral triptans										
Naratriptan	I	DBPC	300	12–17	4-hour HA relief	64%–72%	65%	O	Occasional	65
Rizatriptan	I	DBPC	296	12–17	2-hour pain relief	66%	56%	++	Occasional	66
	I	DBPC	96	6–17	2-hour HA relief	74%	36%			43
Sumatriptan	I	DBPC	302	12–17	2-hour pain relief	NA	NA	0	Occasional	68
Sumatriptan	II	DBPCCO	23	8–16	2 hour >50% decrease	34%	21%	0	Occasional	67
Zolmitriptan	IV	OL	38	12–17	HA improvement	88%	—	+	Occasional	69
	II	DBPCCO	32	11–17	2-hour pain relief	62%	28%	++		63
	I	DBPC	850	12–17	2-hour HA response	53%–57%	58%	0		70
Eletriptan	II	DBPC	267	12–17	2-hour HA response	57%	57%	0	Occasional	71
Almotriptan	IV	OL	15	11–17	HA reduction	85%	—	+	Occasional	72
	I	DBPC	866	12–17	2-hour pain relief	67%	55%	++		44
Sumatriptan	IV	OL	17	6–16	HA response	64%	—	+	Occasional	73
Subcutaneous	IV	OL	50	6–18	HA response	78%	—	+	Frequent 80%	74

Abbreviations: DBPC, double blind placebo-controlled; DBPCCO, double blind placebo-controlled crossover; HA, headache; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OL, open-label; SB, single blind.

[a] Clinical impression of effect: O, ineffective: most patients get no improvement; +, somewhat effective: few patients get clinically significant improvement; ++, effective, some patients get clinically significant improvement; +++, very effective: most patients get clinically significant improvement.

Data from Refs. [63–74]

Only sumatriptan (5 and 20 mg) and zolmitriptan (5 mg) in the nasal spray form and rizatriptan (5 and 10 mg) and almotriptan (6.25, 12.5, and 25 mg) in the tablet form have demonstrated safety and efficacy in controlled trials in adolescents 12 to 17 years of age.[40–45] For young children less than 12 years of age, ibuprofen (7.5–10 mg/kg) and acetaminophen (15 mg/kg) have demonstrated efficacy and safety for the acute treatment of migraine.[46,47] Combination agents, such as sumatriptan, 85 mg, plus naproxen, 550 mg, have demonstrated efficacy in adults, but their utility in adolescents has not yet been demonstrated.[48]

A diverse group of medications is used to prevent attacks of migraine, and it is useful to become comfortable with a few of these agents. Their use should, however, be limited to those patients whose headaches occur with sufficient frequency or severity as to warrant a daily treatment program. Most clinical studies require a minimum of three headaches per month to justify a daily agent. A clear sense of functional disability must be established before committing to a course of daily medication. It is also useful to identify the presence of ''comorbid conditions'' (eg, depression, obesity), which may suggest the relative benefit of one agent over another.

Once preventive treatment is initiated, patience must be encouraged to permit enough time for the beneficial effects to be appreciated. Generally, an 8- to 12-week course is necessary before success or failure can be determined. This point must be emphasized at the time the prescriptions are provided, because many impatient families expect immediate effects after the first days of treatment. The author sees many patients in his practice who have ''failed'' multiple prophylactic courses, only to find that the therapeutic trials lasted for only a few days each.

The duration of treatment is controversial. In recognition of the cyclic nature of migraine, the daily agents should be used for a finite period. The general recommendation is to provide treatment through the calendar school year and then to eliminate daily agents gradually during summer vacation. Another option in younger children is to use a shorter course (eg, 6–8 weeks), followed by slow weaning off the medicine.

For preventive or prophylactic treatment in the population of children and adolescents who have frequent disabling migraine, flunarizine, unavailable in the United States, has established and reproducible efficacy data, but encouraging data are emerging regarding several antiepileptic agents, such as topiramate, disodium valproate, and levetiracetam, in addition to the antihistamine cyproheptadine and the antidepressant amitriptyline (**Table 3**).[49–51]

For children younger than the age of 10 years who do not have problems related to being overweight, cyproheptadine at a starting dose of 2 to 4 mg as a single bedtime dose is a simple and safe strategy. The dose may gradually be elevated to two or even three times a day; however, in the author's experience, most children become too sedated at doses much higher than 4 to 8 mg/d.

Amitriptyline has never been assessed in controlled fashion but remains one of the most widely used agents. Starting doses of 5 to 10 mg at bedtime may gradually be increased toward 1 mg/kg/d. Controversy exists as to whether or not a pretreatment electrocardiogram (ECG) is warranted, but the author generally does not order an ECG for children on low doses (10–25 mg).

Topiramate is gaining wide acceptance, and mounting evidence, based on well-designed controlled trials, supports its use. A 26-week trial of 50-, 100-, and 200-mg doses of topiramate found a reduction in monthly migraine frequency of 46%, 63%, and 65%, respectively, versus 16% with placebo.[52] A second trial evenly randomized 44 children to receive 100 mg divided twice a day versus placebo and found a reduction in the mean monthly migraine attacks from 16 per month to 4 per month in the treatment group versus 13 per month to 8 per month in the placebo group ($P = .025$).[53] In that study,

Table 3
Summary of evidence for the preventive therapies for migraine in children and adolescents

Drug	Class	Study Design	n	Age (Years)	Primary End Point	Efficacy	Placebo Response	Clinical Impression of Effect[a]	Adverse Effects	Reference
Antiepileptics										
Divalproex sodium/ sodium valproate	IV	OL	42	7–16	HA/month	81%	—	+	Occasional to frequent	55
	IV	OL	10	9–17	HA/month	83%	—	+		75
	IV	OL	23	7–17	HA/month	65%> 50% reduction	—	+		76
Gabapentin	IV	Retrospect OL	18	6–17	HA freq/month	83% > 50% reduction	—	++	Occasional to frequent	77
Topiramate	II	DBPC	44	9–17	HA/month	75%	38%	++	Occasional to frequent	53
	I	DBPC	51	12–17	HA/month	54%–67%	42%	+++		52
	I	DBPC	85	12–17	HA/month	76%	45%	+++		54
Levetiracetam	IV	OL	20	6–17	HA/month	90%	—	+	Occasional to frequent	56
	IV	OL	19	Mean 12	HA/month	67%	—	+		57
Zonisamide	IV	OL	12	Mean 13	HA/month	75%	—	+	Occasional	58
Antidepressants										
Trazodone	II	DBPC	35	7–18	HA freq	45%	40%	O	Occasional to frequent	78
Pizotifen	II	DBPCCO	47	7–14	HA/month	15%	16%	O	Occasional to frequent	91
Tricyclic antidepressants										
Amitriptyline	IV	OL	192	9–15	HA freq/month	84%	—	++	Occasional to frequent	79
	IV	OL	73	3–18	HA freq/month	89%	—	++		80
Antihistamines										
Cyproheptadine	II	DBPC	68[a]	17–53	% improve	75%	—	++	Occasional to frequent	81
	IV	Retrospective	30	3–18	HA/month	62%	—	++		80

Calcium channel blockers										
Flunarezine	II	DBPC	42	7–14	>50% improve	76%	19%	+++	Occasional	82
		DBPCCO	63	5–11	HA/month	67%	33%	+++		83
								+++		
Nimodipine	II	DBPCCO	37	7–18	HA/month	15%	16%	O	Occasional	92
Antihypertensive agents										
Propranolol	II	DBPC	39	3–12	HA freq	58%	55%	O	Occasional to	84
	II	DBCO	28	7–16	HA freq	71%	10%	++	frequent	85
	II	DBPC	28	6–12	HA freq	NS	NS	O		86
Timolol	II	DBPCCO	19	6–13	HA/month	38%	40%	O	Occasional	87
Clonidine	II	DBPC	43	7–14	HA/6 weeks	NS	NS	O	Occasional to	88
	II	DBPC	54	<15	HA/month	40%	65%	O	frequent	89
NSAIDs										
Naproxen sodium	III	DBPC	10	6–17	HA freq	60%	40%	+	Occasional	90

Abbreviations: DBPC, double blind placebo-controlled; DBPCCO, double blind placebo-controlled crossover; freq, frequency; HA, headache; IV intravenous; NSAID, nonsteroidal anti-inflammatory drug; OL, open-label; NS, not significant.

[a] Clinical impression of effect: O, ineffective: most patients get no improvement; +, somewhat effective: few patients get clinically significant improvement; ++, effective: some patients get clinically significant improvement; +++, very effective: most patients get clinically significant improvement.

Data from Refs. [75–92]

there was a significant reduction in overall disability and school absenteeism. A third recent report comparing 50 mg/d versus 100 mg/d versus matched placebo found a statistically significant improvement from the prospective baseline period in migraine frequency with the 100-mg dose (75% decrease in monthly migraines) but not with the 50-mg dose (46% decrease in monthly migraines) or in the placebo group (45%) ($P = .016$). The most benefit was appreciated in 100-mg group (50 mg administered orally twice a day), in which it was observed that more than 80% of patients experienced a greater than 50% reduction in headache burden after approximately 8 weeks of treatment.[54]

Typically, for teenagers, a 15- to 25-mg dose of topiramate is initiated as a single bedtime dose and then gradually titrated toward 50 mg twice a day incrementally on a weekly or every-other-week basis. Clinical experience has demonstrated that many patients respond to doses as low as 25 mg given at bedtime; thus, it is valuable to "titrate to effect." Cognitive effects must be monitored quite carefully, and more evidence is needed to assess the educational impact of topiramate for prevention of adolescent migraine. It is counterproductive to reduce the headache burden at the expense of academic performance.

Divalproex sodium has strong efficacy data in adults and is approved for use as a migraine preventative agent, but no controlled trials exist in children or adults. Open-label trials have had success. In one study of 42 children (aged 7–16 years, mean age = 11.3 years), a 50% headache reduction was seen in 78.5%, a 75% headache reduction was seen in 14.2%, and 9.5% of patients became headache-free. These open-label results indicated that divalproex sodium was an effective and well-tolerated treatment for the prophylaxis of migraine in children.[55]

Likewise, levetiracetam has open-label data from 19 patients (mean age = 11.9 years) whose mean migraine frequency fell from 6.3 migraines per month to 1.7 per month at doses of 125 to 250 mg given twice a day. Ten patients (52.6%) had complete resolution of headache. The investigators concluded that levetiracetam seemed to be a promising candidate for well-controlled clinical trials of pediatric patients who have migraine.[56] A second open-label trial of 20 patients found that 18 of 20 patients had a 50% or greater reduction in monthly migraine frequency and had lowered disability scale scores at doses of approximately 20 mg/kg/d.[57]

In one small open-label study in children (10–17 years of age) with mixed refractory headache conditions (50% migraine), the children were treated with zonisamide at an average dose of 6 mg/kg/d.[58] Two thirds of the children had a greater than 50% reduction in headache frequency from baseline.

PROGNOSIS

The long-term prognosis of adolescents who have migraine has not been well studied. Five- to 7-year follow-up studies revealed that 20% to 25% of adolescents originally diagnosed with migraine have remission of symptoms, 50% to 60% have persistence of their migraine with aura, and 25% convert to tension-type headache (TTH). Twenty percent who originally had TTH converted to migraine.[59,60] Monastero and colleagues[61] evaluated 55 adolescents with migraine who were available for 10 years of follow-up and found that 42% had persistent migraine, 38% had experienced remission, and 20% had transformed to TTH. Interestingly, only migraine without aura persisted through the 10-year follow-up period, whereas other migrainous disorders and nonclassifiable headaches did not. The longest follow-up available came from Brna and colleagues,[62] with 20-year information on 60 members of an original cohort of 95 from 1983. Of the 60, 27% were headache-free, 33% had TTH, 17%

had migraine, and 23% had TTH and migraine. Of those with persistent headache, 80% described their headaches as moderate to severe, although an overall improvement was described in 66%. TTH was more likely to remit. Headache severity at diagnosis was the most predictive of headache outcome at 20 years. These data indicate that female gender, migraine severity at diagnosis, and longer duration from time of onset of headache until time of initial medical examination tended toward an unfavorable prognosis. Given our current understanding of the long-term neuropathologic and psychosocial consequences of persistent frequent migraine, further longitudinal epidemiologic study of the evolution of adolescent migraine is imperative.

SUMMARY

Migraine is a common disorder in children and adolescents. There is a wide spectrum of clinical forms, but the most frequent form is migraine without aura, which is characterized by attacks of frontal or bitemporal pounding and nauseating headache lasting 1 to 72 hours. A fascinating and challenging subset known as migraine with aura and the periodic syndromes can be associated with frightening focal neurologic disturbances and may require careful consideration for the possibility of neoplastic, vascular, metabolic, or toxic disorders.

Migraine treatment philosophy now embraces a balanced approach with biobehavioral interventions and pharmacologic measures. Treatment decisions must be based on the disability produced by the headaches, the headache burden. A growing body of controlled pediatric data is beginning to emerge regarding the acute and preventative agents, lessening our dependence on extrapolated adult data.

In the near future, we anticipate further advances in understanding the molecular genetics of migraine, advances that should translate to improved care of the pediatric patient who has migraine headache. Furthermore, therapeutic energy expended for our pediatric patients should translate to decreased disability as our patients progress into adulthood, lessening the lifespan burden of migraine.

APPENDIX

Box A1
American Academy of Neurology evidence classification scheme for a therapeutic article and linkage to level of recommendation (2003 version)

Rating of therapeutic article

Class I: prospective, randomized controlled, clinical trial with masked outcome assessment, in a representative population

Class II: prospective matched group cohort study in a representative population with masked outcome assessment that meets a through d or a randomized clinical trial in a representative population that lacks one criterion

Class III: all other controlled trials in a representative population, in which outcome is independently assessed or independently derived by objective outcome measurement

Class IV: evidence from uncontrolled studies, case series, case reports, or expert opinion

In exceptional cases, one convincing class I study may suffice for an "A" recommendation if (1) all criteria are met, (2) there is a magnitude of effect of 5 or greater, and (3) there are narrow confidence intervals (lower limit >2).

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