This review focuses on so-called “periodic syndromes of childhood that are precursors to migraine,” as included in the second edition of the International Classification of Headache Disorders. Presentation is characterized by an episodic pattern and intervals of complete health. Benign paroxysmal torticollis is characterized by recurrent episodes of head tilt, secondary to cervical dystonia, with onset between ages 2-8 months. Benign paroxysmal vertigo presents as sudden attacks of vertigo lasting seconds to minutes, accompanied by an inability to stand without support, between ages 2-4 years. Cyclic vomiting syndrome is distinguished by its unique intensity of vomiting, affecting quality of life, whereas abdominal migraine presents as episodic abdominal pain occurring in the absence of headache. Their mean ages of onset are 5 and 7 years, respectively. Diagnostic criteria and appropriate evaluation represent the key issues. Therapeutic recommendations include reassurance, lifestyle changes, and prophylactic as well as acute antimigraine therapy.

Periodic Syndrome

In 1933, Wyllie and Schlesinger introduced the term “periodic disorder of childhood” to describe recurrent episodes of pyrexia, headache, vomiting, and abdominal pain in childhood, and reported that the signs persisted in adult life as migraine or bilious attacks. In Australia, Cullen and MacDonald noted that periodic syndrome frequently occurred in children with a family history of migraine. In Boston, Barlow confirmed that periodic syndrome was a common childhood precursor of adult migraine. Only recently has there been more widespread acceptance of the existence of childhood periodic syndromes as a migraine variant in children.

Evidence that childhood periodic syndromes may constitute a migraine phenomenon relies on several separate strands of evidence. Signs pertaining to childhood periodic syndromes frequently coexist with migraine headaches. There are similarities between children with childhood periodic syndromes and children with migraine headaches, with respect to social and demographic factors, precipitating and relieving factors, and accompanying gastrointestinal, neurologic, and vasomotor features. Children with childhood periodic syndromes commonly exhibit a family history of migraine, and childhood periodic syndromes follow a well-known tendency to transform into migraine headaches by several years. Some of these entities were formerly known as “migraine equivalents.” Nowadays, they are called “childhood periodic syndromes.” In the most recent criteria, i.e., the International Classification of Headache Disorders, Second Edition, childhood periodic syndromes appear as a ubiquitous group termed “childhood periodic syndromes that represent precursors of migraine,” under Migraine Subtype 1.3. Our review mainly focuses on the childhood periodic syndromes included in the International Classification of Headache Disorders, Second Edition.

Introduction

The outstanding feature of migraine in any of its manifestations is its paroxysmal or periodic occurrence. There is always a return to baseline, with resulting sign-free intervals. It has long been recognized that migraine is not merely a syndrome of headache, but that the headache is associated with a range of other signs, e.g., vertigo, torticollis, and visual and sensorimotor disturbances, and gastrointestinal features, e.g., anorexia, abdominal pain, nausea, and vomiting. In some patients, these signs may occur in the absence of headache, and the attacks may precede the development of migraine headaches by several years. Some of these entities were formerly known as “migraine equivalents.” Nowadays, they are called “childhood periodic syndromes.” In the most recent criteria, i.e., the International Classification of Headache Disorders, Second Edition, of the International Headache Society, childhood periodic syndromes appear as a ubiquitous group termed “childhood periodic syndromes that represent precursors of migraine,” under Migraine Subtype 1.3. Our review mainly focuses on the childhood periodic syndromes included in the International Classification of Headache Disorders, Second Edition.
headaches as a child matures. Mortimer and Good [7] demonstrated that children with childhood periodic syndromes exhibited visual-evoked responses similar to those of children with migraine. The final strand of evidence involves the effectiveness of nonanalgesic migraine therapy in childhood periodic syndromes.

The key clinical features of this group of disorders include the episodic, reversible, and stereotyped nature of attacks. Children with childhood periodic syndromes are completely healthy between attacks and, in contrast, are extremely unwell during attacks. Childhood periodic syndromes represent challenges for the clinician, because clinical diagnosis and epidemiologic research may well be of the utmost difficulty. The differential diagnosis of disorders that can mimic childhood periodic syndromes is extensive, and includes inborn errors of metabolism, including mitochondrial disorders, and channelopathies. Thus, a diagnosis of childhood periodic syndromes is one of exclusion, and involves extensive diagnostic testing to exclude other discernable causes (e.g., epilepsy, metabolic disorders, ischemic events, or psychogenic causes). Thus a diagnosis can only be rendered after a careful history-taking, physical examination, and appropriate neurodiagnostic studies. Finding an appropriate balance between the high costs of complete testing and the potential morbidity of a missed treatable underlying disorder presents a rigorous test of clinical judgment. Furthermore, it is important to make a definite diagnosis in the presence of classic findings. Finally, childhood periodic syndromes can often be correctly classified only after the recurrence of an episode.

Three childhood periodic syndromes are included in the International Classification of Headache Disorders, Second Edition: abdominal migraine, cyclic vomiting syndrome, and benign paroxysmal vertigo [1]. A fourth childhood periodic syndrome, benign paroxysmal torticollis, is not included in the International Classification of Headache Disorders, Second Edition, but is presented in its Appendix [1]. Recent molecular genetic data provide increasing evidence for benign paroxysmal torticollis as a “precursor” of migraine (see below).

Because of three factors (the unknown pathophysiology, the absence of controlled drug trials, and a placebo response as high as 70%), therapy remains empiric rather than evidence-based [8]. These therapies include the avoidance of potential triggers, prophylactic pharmacologic therapy, abortive pharmacologic therapy, supportive care during an episode, and general family support.

Benign Paroxysmal Torticollis of Infancy

Benign paroxysmal torticollis is a rare paroxysmal dyskinesia characterized by recurrent stereotypic attacks of torticollis, first described by Snyder in 1969 [9]. About 50 cases have been reported since 1969, but missed diagnoses are likely [10]. There is a female preponderance (about 70%) [10]. During an attack, abnormal inclination or rotation of the head to one side occurs by itself, or is accompanied by vomiting and ataxia. Torticollis may occur on either side. Other torsional or dystonic features, including truncal or pelvic asymmetrical posturing, or retrocollis, were described [11]. In some cases, an abrupt turning of the head and eyes to one side, rapid blinking, flexing of the upper limbs, upward-diverted gaze [12], palpebral ptosis, and mydriasis on the same side occurred. Benign paroxysmal torticollis is often accompanied by signs similar to some of the nonheadache features of migraine, including pallor, hypotonia of one limb, photophobia, tears, ataxia, apathy, and drowsiness, in addition to headache. Onset is sudden, without warning, and with a spontaneous resolution of episodes. The episodes most often last hours to days, but may last only a few minutes in some patients. Attacks first manifest during infancy, between ages 2-8 months. They resolve by age 3-5 years [13]. Typically, the frequency and duration of attacks decline as the child grows older.

Table 1 lists the criteria of the International Classification of Headache Disorders, Second Edition, for benign paroxysmal torticollis. The differential diagnosis includes gastroesophageal reflux (Sandler’s syndrome), idiopathic torsional dystonia, complex partial seizure, and especially posterior fossa tumors and craniofascial junction dysfunction.

Drigo et al. [10] postulated that benign paroxysmal torticollis included two differential situations. They referred to the more common as “periodic” torticollis, in which attacks last several hours or days. The rarer situation is short-lived and “paroxysmal,” lasting only minutes, and is accompanied by ocular signs generally lacking in the periodic version [10].

Beyond the common finding of a family history of motion sickness or migraine [10], patients with benign paroxysmal torticollis may develop benign paroxysmal vertigo, cyclic vomiting syndrome, abdominal migraine, motion sickness, or migraine.

The etiopathogenesis of benign paroxysmal torticollis is unknown. Some authors suggest an underlying vestibular disorder such as labyrinthitis [9,14]. Others claim an involvement of the central vestibular region or vestibulocerebellar connections [12,15,16]. Perhaps an immaturity of the brain or of some neurotransmitters is involved during a limited period of life. The hypothesis of a channelopathy was raised. This entity was more recently linked to a mutation in the CACNA1A gene [13]. Giffin et al. [13] suggested that the cerebellar cortex, where the CACNA1A gene is abundantly expressed, probably contributes to the expression of benign paroxysmal torticollis. Moreover, a decrease of glucose metabolism in the cerebellar cortex and basal ganglia, and a decrease of perfusion in the basal and temporal cortex, were demonstrated by John et al. [17].

If the episodes recur, their management is unclear. No clinical trials have been reported. The question remains of whether these events, after they are found to be benign, require any treatment beyond reassurance. Some authors suggest a trial of cyproheptadine as a safe measure that may provide some benefit if an individual’s episodes are painful [18].
Benign Paroxysmal Vertigo of Childhood

Described for the first time by Basser in 1964, benign paroxysmal vertigo usually presents in young children as episodes of unexplained fright associated with balance troubles or even falls [19]. The suggested prevalence is 2-2.6% [20,21]. The sex distribution is equal.

Onset is sudden (95%) [22], with an expression of anxiety and fear on the face of the child, who may grasp a person standing nearby or any other support, or else may sway or refuse to stand. Ataxia may remain unnoticed, because some children will refuse to leave their beds. Infants may cry. Verbal children may report dizziness and nausea. Attentive parents may also report nystagmus. Neurovegetative signs may also occur, e.g., pallor, nausea, perspiration, photophobia, phonophobia, and unusual head positions. Vomiting is rather frequent, and may be vigorous. There is never any loss of consciousness, but in some children, an episode may evolve to syncope. The duration of episodes is generally brief (less than 5 minutes, and sometimes even a few seconds), but may rarely last a few hours, with an extreme of 48 hours. The episode typically resolves with sleep, although other authors claim that falling asleep after an episode is rare [22]. In other cases, relief may come from lying or sitting down. The onset is between age 2-4 years, with extremes of 5 months to 8 years [22,23]. The frequency of episodes varies from once a day to once every 1-3 months. They tend to recur more frequently at first, and to become rarer with time and increasing age. The spells may occur in clusters over several days, and then subside for weeks or months [19,24]. Trigger factors include round-

Table 1. ICHD-II criteria for benign paroxysmal torticollis of childhood

<table>
<thead>
<tr>
<th>A1.3.5. Benign paroxysmal torticollis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Episodic attacks, in a young child, with all of the following characteristics and fulfilling criterion B:</td>
</tr>
<tr>
<td>1. Tilt of the head to one side (not always the same side), with or without slight rotation</td>
</tr>
<tr>
<td>2. Lasting minutes to days</td>
</tr>
<tr>
<td>3. Remitting spontaneously and tending to recur monthly</td>
</tr>
<tr>
<td>B. During attacks, signs of one or more of the following:</td>
</tr>
<tr>
<td>1. Pallor</td>
</tr>
<tr>
<td>2. Irritability</td>
</tr>
<tr>
<td>3. Malaise</td>
</tr>
<tr>
<td>4. Vomiting</td>
</tr>
<tr>
<td>5. Ataxia</td>
</tr>
<tr>
<td>C. Normal neurologic examination between attacks.</td>
</tr>
<tr>
<td>D. Not attributed to another disorder.</td>
</tr>
</tbody>
</table>

Abbreviation:
ICHD-II = International Classification of Headache Disorders, Second Edition

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Table 2 lists the criteria for benign paroxysmal vertigo in the International Classification of Headache Disorders, Second Edition. The differential diagnosis should include benign positional paroxysmal vertigo and episodic ataxia. Benign positional paroxysmal vertigo is the most frequent labyrinthopathy in humans, and is caused by a massive detachment of otoliths from the utricular macula, although it is rare in children. A diagnosis of episodic ataxia should prompt a trial of acetazolamide. The clinician should also exclude epilepsy, neurinomas and tumors of the pontocerebellar angle or posterior fossa, Ménière’s disease, and vestibular neuritis. Benign paroxysmal vertigo should also be differentiated from the idiopathic vertigo that may occur abouts, swings, and seesaws, i.e., means of stimulating the labyrinth, but may also include awakening, fever, tiredness, or stressful events [22].

A positive family history of migraine is frequently found, but surprisingly, a meta-analysis of six benign paroxysmal vertigo studies that included 86 children found a prevalence of family history of migraine at 36%, i.e., a figure clearly lower than in patients with migraine [23]. A family history of motion sickness is also frequent, e.g., 83% according to Drigo et al. [22]. A personal history of motion sickness is common [22], as well as atopic disease [20]. Abu-Aræf and Russell studied the prevalence of benign paroxysmal vertigo in the well-defined childhood population of Aberdeenshire, Scotland, and found a greater prevalence of migraine in benign paroxysmal vertigo patients (24% versus 10.6%), and of benign paroxysmal vertigo in migraine patients (8.8% versus 2.6%), than in control subjects [20].

Some authors suggest that benign paroxysmal vertigo constitutes an early-onset variant of basilar-type migraine [18]. According to Lindskog et al., benign paroxysmal vertigo would consist of two entities [23]. One would be a migraine equivalent with a family history of migraine, and the other, a more pure form without any relation to migraine. Benign paroxysmal vertigo is probably underdiagnosed because of the brief duration of attacks and their benign nature.

Electroencephalogram tracings in waking and sleeping states, as well as during an episode, are normal. Audiologic examinations, including impedance measurement with stapedial reflex, always produce negative results. Regarding the results of vestibular examination, the vestibular hyporeactivity suggested by Basser [19] was not confirmed in subsequent reports. Some authors reported the presence of nystagmus or of unilateral or bilateral vestibular hypofunction with caloric stimulation [19,25,26], but these data were not confirmed by other authors [27,28]. In the patients of Marcelli et al., vestibular examination produced positive results in three patients with a negative Dix-Hallpike maneuver [29]. The vestibular examinations have consequently failed to help explain the etiopathogenesis of the disorder, considered by some authors [30] as a peripheral vestibular dysfunction, and by others [31] as a central vestibular problem, with a deficiency of the vestibular nuclei or of the vestibular-cerebellar pathways [32].
1.3.3. Benign paroxysmal vertigo of childhood

A. At least five attacks fulfilling criterion B.
B. Multiple episodes of severe vertigo, occurring without warning and resolving spontaneously after minutes to hours.
C. Normal neurologic examination; audiometric and vestibular functions between attacks.
D. Normal electroencephalogram.

Abbreviation:
ICHD-II = International Classification of Headache Disorders, Second Edition

Abdominal Migraine and Cyclic Vomiting Syndrome

Abdominal Migraine

Abdominal migraine was first described by Buchanan in 1921 as attacks of abdominal pain in the absence of headache [34]. The following year, Brams introduced the term “abdominal migraine” [35]. Blau and MacGregor called for a more precise definition of what was meant by the term “abdominal migraine” [36]. In 2001, Dignan et al. offered an extended definition [37]. Although abdominal migraine remains a controversial issue, it was included for the first time in the International Classification of Headache Disorders, Second Edition [1], which provided alternative criteria (Table 3).

Abdominal migraine is characterized by recurrent, acute-onset, incapacitating, noncolicky midline abdominal pain lasting for hours, accompanied by pallor, dark shadows under the eyes, flushing, and anorexia. Abdominal pain is often described as “just sore” or “dull” (60%), but can be colicky (22%) [38]. It is periumbilical in most patients (78%), but can be felt diffusely (16%) [38]. It interfered with normal daily activities in 72% of the patients of Abu-Arefeh and Russell [38]. Patients with abdominal migraine tend to experience more social withdrawal and phobias with episodes, and are more likely than patients with cyclic vomiting syndrome to manifest triggering events such as psychologic stress, physical exhaustion, and motion sickness. Vomiting may constitute an accompanying feature, but is often less severe that in cyclic vomiting syndrome. Children with abdominal migraine are completely healthy between attacks, and in contrast, are extremely unwell during attacks, which are separated by sign-free intervals of weeks to months. Usually a history of migraine headache is evident either in the child or the family, but headache may be minimal or absent during attacks. Abdominal migraine occurs more commonly in children, with a mean age at onset of abdominal migraine of 7 years [38], with peak prevalence at age 10 years [39]. Abdominal migraine thereafter declines rapidly. The estimates of prevalence in childhood range from 2.4-4.1% [38,40]. It is more common in girls.

The onset and resolution of signs are sudden [41]. Occasionally, they are preceded by nonspecific prodromal signs, such as behavior or mood changes or anorexia (14%) [38]. Sometimes, a preceding aura occurs involving visual disturbance, flashing lights, numbness or a tingling sensation, slurred speech, or muscle weakness. In some children, the attacks are stereotypical, with identical attacks occurring at regular intervals, although more often,
1.3.2 Abdominal migraine

A. At least five attacks fulfilling criteria B-D.

B. Attacks of abdominal pain lasting 1-72 hours (untreated or unsuccessfully treated).

C. Abdominal pain has all of 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.

Abbreviation:
ICHD-II = International Classification of Headache Disorders, Second Edition

Table 3. ICHD-II criteria for abdominal migraine

Cyclic Vomiting Syndrome

Cyclic vomiting syndrome is characterized by recurrent, discrete, self-limited episodes of severe nausea and vomiting, interspersed with sign-free periods. It was described by Gee in the English-language literature in 1882 [47], and in 1806 by Heberden in the French literature [48]. It
is defined by sign-based criteria and the absence of positive laboratory, radiographic, and endoscopic testing. Cyclic vomiting syndrome is described in all races and ethnicities, but affected children are more often girls than boys (60:40). Cyclic vomiting syndrome is more often reported in children of Northern European ancestry [49]. Pediatric cyclic vomiting syndrome was reported to exhibit a prevalence of 0.04-1.9% of children, with an incidence of new cases at approximately 3 per 100,000 children per year [3,49,50]. Because of discrepancies in methodology between these prevalence studies, the true prevalence of cyclic vomiting syndrome is probably somewhere between these two values. Thus cyclic vomiting syndrome comprises the second most common cause of recurrent vomiting in children, after gastroesophageal reflux [49]. The average age at initial diagnosis is 5 years (range, 4.6-5.3 years), but cyclic vomiting syndrome occurs in all age groups, including adults. The youngest age of onset reported so far is 6 days and the oldest reported is 73 years. However, the diagnosis is typically delayed for several years (range, 2.6-3.1 years) [8,49,51]. A family history of migraine is present in 67-82% of patients [49,52]. A large series found that cyclic vomiting syndrome resulted in 24 days of missed school and an annual cost of care at $17,035 per patient [8].

Affected children usually experience a stereotypical pattern of vomiting, typified by a consistent time of onset, duration, and signs. The clinical picture of cyclic vomiting syndrome can be divided into four phases: (1) an interepisodic phase, (2) a prodromal phase, (3) an emetic phase, and (4) a recovery phase [8,49,51,53]. During the interepisodic phase, the patient has relatively few signs. The prodromal phase lasts a median of 1.5 hours, and is heralded when the patient senses an impending episode that evolves to nausea, accompanied by dramatic autonomic dysfunction, decreased muscle tone, pallor, and lethargy or apathy, causing total incapacitation throughout the duration of the emetic phase. Typically, during the prodromal phase, the child can still take and retain oral medications. The emetic phase lasts a median of 41 hours, and a median of 24 hours [8,49,51,53]. The vomiting is intense (a median of 6 times/hour at peak, but may be more than 10 times/hour), is often bilious, and is accompanied by disabling and persistent nausea. The accompanying signs include anorexia, nausea, retching, increased salivation, abdominal pain, headache, pallor, listlessness, photophobia, and phonophobia. Signs of an intense stress response are also common, including increased heart rate and blood pressure, drenching diaphoresis, low-grade fever, and neutrophilia. Patients may become irritable, verbally abusive, demanding, and prone to social withdrawal. The recovery phase begins as soon as the nausea remits, and ends with a resumption of normal appetite, oral intake, and baseline clinical status. It is a remarkably brief 6 hours, often typified by sleep. It is important in clinical practice to recognize this phasic pattern, because it may have consequences in terms of diagnosis as well as management [8,49,51,53]

Episodes often commence in the early morning or upon awakening, and are frequently triggered by psychologic (e.g., birthdays, school-related issues, or emotional excitement) and physical (e.g., infections or lack of sleep) stress. The duration of a total episode ranges between 2 hours and 10 days (mean, 2 days). Prakash et al. observed that episodes lengthened progressively from childhood to adulthood, starting from 1.8-3.9 days [51]. Affected children generally undergo 4-12 episodes per year.

The median age of resolution of vomiting episodes is 10 years [49]. A prediction analysis by Li and Misiewicz estimated that 75% would develop migraines by age 18 years [49]. Less commonly, the condition persists into adulthood, or begins in adulthood [52,54].

Diagnostic Approach

A diagnosis is based on a typical clinical presentation, and by the exclusion of other possible causes with a similar presentation [55]. Table 4 lists the criteria of the International Classification of Headache Disorders, Second Edition, for cyclic vomiting syndrome (Table 4). In the absence of controlled trials and high-quality scientific evidence regarding the disorder, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition developed its operational definition of cyclic vomiting syndrome, to improve the recognition and treatment of cyclic vomiting syndrome [53]. A pattern of recurrent, episodic vomiting in children that fulfills the criteria of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition is about 90% likely to be diagnosed ultimately as idiopathic cyclic vomiting syndrome. The challenge for the practitioner is to differentiate individuals with specific and serious underlying causes of vomiting for which prompt treatment may alter outcomes. A diagnostic algorithm of cyclic vomiting syndrome is thus based on the fulfillment of criteria in the absence of another explanation for the given signs. Clinicians experienced in evaluating cyclic vomiting syndrome may treat without performing an extensive evaluation, whereas those less accustomed to cyclic vomiting syndrome may be more anxious to perform an extensive, detailed evaluation. Using decision-analysis software, Olson and Li [56] performed a comparison of the cost-effectiveness of extensive diagnostic evaluation, empiric treatment alone, and upper gastrointestinal radiology with small-bowel follow-through plus empiric treatment. Upper gastrointestinal radiology with small-bowel follow-through plus empiric antimigraine treatment for an initial period of 2 months was the most cost-effective strategy.

A thorough history and physical examination at presentation help identify physical findings [53], including:

- Bilious vomiting, abdominal tenderness, and/or severe abdominal pain;
- Attacks precipitated by intercurrent illness, fasting, and/or high-protein meals;
Table 4. ICHD-II criteria for cyclical vomiting

1.3.1 Cyclical vomiting

A. At least five attacks fulfilling criteria B and C.

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

C. Vomiting during attacks occurs at least 4 times/hour for at least 1 hour.

D. Sign-free between attacks.

E. Not attributed to another disorder.

Abbreviation:
ICHDI-II = International Classification of Headache Disorders, Second Edition

- Abnormalities on neurologic examinations, including severe alteration of mental status, abnormal eye movements, papilledema, motor asymmetry, and/or gait abnormality (ataxia); and
- Progressively worsening episodes, or conversion to a continuous or chronic pattern.

Although children below age 2 years may exhibit cyclic vomiting syndrome, serious underlying metabolic and surgical disorders are more frequent, and are more difficult to diagnose in that age range.

Bilious emesis or severe abdominal pain should raise the possibility of intermittent bowel obstruction from malrotation with volvulus and postoperative adhesions/strictures, gallbladder disease, choledochal cysts, hepatitis, pancreatitis, or a ureteropelvic junction obstruction. An esophagogastroduodenoscopy should be performed in cases of recurrent episodes of vomiting accompanied by hematemesis. Vomiting induced by fasting, acute illness, or a high-protein meal should lead to suspicions of a metabolic disorder, e.g., disorders of fatty-acid oxidation, the urea cycle, organic and amino-acid metabolism, respiratory alkalosis, and mitochondrial energy metabolism. Progressive or focal neurologic findings, as well as new-onset ataxia, abnormal eye movements, papilledema, motor asymmetry, gait abnormality, developmental regression or stagnation, or recent personality changes, should lead the clinician to suspect increased intracranial pressure or a metabolic disorder, warranting magnetic resonance imaging. Munchausen-by-proxy syndrome may sometimes mimic cyclic vomiting syndrome.

Treatment

An initial trial of empiric therapy can be considered in children with a cyclic pattern of vomiting and no alarming findings in their history and physical examination. If a patient does not improve with this initial therapy during a 2-month period, a statement by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition on the diagnosis and management of cyclic vomiting syndrome recommends further evaluation [53].

The management of cyclic vomiting syndrome requires an individually tailored regimen that takes into consideration the clinical course, frequency, and severity of attacks and the resultant disability, balanced against the potential side effects of treatment. Treatment is often a trial-and-error process. The two important arms of treatment include prophylactic measures and medications administered between attacks, and acute and supportive interventions given during attacks. In the absence of medications approved by the United States Food and Drug Administration for use in children with cyclic vomiting syndrome, the recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition include off-label uses [53].

First, precipitating factors should be identified and corrected. In some instances, the avoidance of precipitating factors such as dietary chocolate or cheese can prevent episodes altogether, without the use of prophylactic medications. Oral contraceptive pills were used to help prevent episodes triggered by menses. In anxiety-prone patients, helping them recognize anticipatory anxiety and adopting behavioral self-management techniques are important. When a sleep pattern is altered, restoration of a normal sleep pattern aids in preventing attacks.

If abortive therapy fails consistently, or episodes are frequent or severe, then daily prophylactic therapy to prevent subsequent episodes is recommended. Prophylactic agents to treat cyclic vomiting syndrome include antimigraine, antiepileptic, and prokinetic agents (e.g., erythromycin). A task force of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommended cyproheptadine or propranolol as first choice in children aged 5 years and younger [53]. In older children, the task force recommended amitriptyline or propranolol. Prophylactic therapy is justified when episodes occur more frequently than once a month, are difficult to abort, or are particularly severe and disabling.

Abortive therapy should be used during the prodromal phase, when the patient begins to sense early nausea signaling the approach of vomiting. Patients usually prefer a dark and quiet environment. Both antimigraine and antiemetic agents were used as abortive medication [53]. Sumatriptan may be effective in people with a migraine diathesis and a family history of migraine [53]. Antiemetic agents such as ondansetron and promethazine, in combination with diphenhydramine, have been successful. Benzodiazepines may terminate the episode by inducing sleep. If a full-blown vomiting phase occurs, supportive therapy at home or in hospital focuses on relief from nausea, vomiting, and abdominal pain. The role of adequate intravenous hydration cannot be overemphasized [53]. Electrolytes should be monitored closely, and replaced as needed. Adequate care includes intravenous fluids containing 10% dextrose or
normal saline, treatment of nausea with antiemetics and sedatives, and management of abdominal pain.

Supportive care is required when both prophylactic and abortive pharmacologic therapies fail. Family support is crucial to deal with the high level of family frustration when coping with an unpredictable, disruptive, unexplained illness that is typically misdiagnosed, and for which there are few definitive answers. The help of a mental-health professional experienced with cyclic vomiting syndrome can be useful for the entire family in selected patients [8]. Families should be strongly encouraged to obtain information from one of several available online and print sources, and to seek consultation from a pediatric specialist familiar with the management of cyclic vomiting syndrome.

Similarities Between Abdominal Migraine and Cyclic Vomiting Syndrome

Similarities between both abdominal migraine and cyclic vomiting syndrome, and migraine, occur in terms of demographic features, associated recurrent conditions, precipitating triggering factors, associated signs during attacks, and relieving factors [3,43]. Both cyclic vomiting syndrome and abdominal migraine are relatively unusual conditions, and lack specific diagnostic features. When both occur in the same patient, the core signs of vomiting and abdominal pain not only differentiate these two entities, but also seem to dictate which primary label should be used (e.g., abdominal pain in abdominal migraine). The key difference between cyclic vomiting syndrome and abdominal migraine involves a family history of migraine headache. Usually a family history of migraine is present in abdominal migraine, particularly in the mother [39].

Other Childhood Periodic Syndromes

Beyond the childhood periodic syndromes described above, other clinical entities are not yet universally accepted by neurologists, and are not included in the International Classification of Headache Disorders, Second Edition. Although these clinical entities need further validation by longitudinal data collection, and although their relationship to migraine remains uncertain, we have chosen to discuss two of them briefly in this review: cyclic vomiting syndrome plus, and recurrent limb pain.

Cyclic Vomiting Syndrome Plus

Although most children with cyclic vomiting syndrome are otherwise healthy and of normal intelligence, a significant subset exhibits coexisting neuromuscular disorders, e.g., cognitive disorders, myopathy, cranial-nerve abnormalities, and seizure disorders [57]. Boles et al. coined the term “cyclic vomiting syndrome plus” to designate this subset [58]. There is no greater degree of severity in terms of the frequency, duration, or response to pharmacologic therapy for vomiting episodes in cyclic vomiting syn-
drome compared with cyclic vomiting syndrome plus. Cyclic vomiting syndrome plus is also associated with a younger age at onset of vomiting episodes.

Patients with cyclic vomiting syndrome plus manifest many of the neuromuscular conditions frequently reported in individuals with mitochondrial disease, and may also demonstrate lactic acidosis, energy-depleted patterns on urine organic acid analysis, and abnormal muscle biopsy data. Moreover, maternal inheritance in most cases of cyclic vomiting syndrome plus [59], along with mitochondrial DNA mutations in some [60,61], strongly suggests that cyclic vomiting syndrome plus is a mitochondrial disease. Boles et al. proposed that those individuals diagnosed with cyclic vomiting syndrome plus would stand at the most severe end of the spectrum, and therefore would exhibit the highest degree of mitochondrial dysfunction [58].

Patients with cyclic vomiting syndrome plus do not differ from those with cyclic vomiting syndrome in terms of response to prophylactic antimigraine therapies, e.g., amitriptyline, cyproheptadine, and propranolol. The small numbers reported for each therapeutic agent do not allow for a careful evaluation of the efficacy of the various treatment modalities. According to the clinical experience of Boles et al., vomiting episodes respond in most cases to a combined antimigraine and antimitochondrial dysfunction treatment approach [58]. Nevertheless, in addition to the usual recommendations for cyclic vomiting syndrome, based on the frequent occurrence of fasting intolerance in patients with mitochondrial disorders and the frequent occurrence of fasting intolerance in patients with cyclic vomiting syndrome with or without neuromuscular disease, the practitioner should advise frequent feedings as part of prophylaxis, and the early use of 10% intravenous dextrose-containing fluids (instead of the standard 5%) during vomiting episodes requiring medical treatment.

Recurrent Limb Pain

Recurrent limb pain presents as recurrent short episodes of limb pains lasting for less than 72 hours and severe enough to disrupt normal daily activities. It is often localized deeply in the arm and legs, and presents a broad distribution in the extremities. No abnormality and no identifiable underlying organic cause are evident on clinical examination. The condition runs a benign and self-limiting course. It may sometimes be referred to as “growing pains.” Many of these children exhibit limb pain as their only sign, but about one third also complain of abdominal pain and headache. An epidemiologic, population-based study conducted in Aberdeen among 2165 schoolchildren aged 5-15 years indicated that recurrent limb pain was evident in 2.6% of schoolchildren [62]. Episodes of pain occurred, on average, 12 times per year, and each episode lasted an average of 10 hours. The most common triggering factor was tiredness. Other triggering factors included a change of weather, or exposure to cold conditions, e.g., when skiing. The limbs tend to become cold and pallid at
the onset of pain. Associated features include anorexia and nausea. The pain was relieved by rest, simple analgesics, or sleep, or by rubbing the affected limb. A history of migraine in a first-degree relative is as common in children with recurrent limb pain as in children with migraine headache, and was much more common than in a matched control group of children [62].

A familial case of limb pain was reported by Saito et al. [63]. One of the affected family members was an infant whose first attack occurred at age 6 months. These attacks occurred 5-15 days per month, and lasted from 2 hours to all day. The pain was pressure-type and not pulsating. The clinical course was identical among affected family members, including the amelioration of limb pain and the emergence of migraine during adolescence. Thermography performed during the pain attack showed that the temperature was lower in the aching foot, compared with the contralateral side at the onset of pain. Elevated plasma substance P and calcitonin gene-related peptide levels were detected in the presence of limb pain. An abnormal release of calcitonin gene-related peptide and substance P in the vascular walls of the extremities may be cardinal in the pathophysiology of the limb pain, as is also the case in the trigeminovascular theory of migraine.

Pathophysiology

The unusual features evident during the aura phase of a migraine attack are thought to be attributable to the transient effects of “cortical spreading depression,” wherein a region of the cerebral cortex is temporarily and reversibly disturbed and suppressed [64]. During the aura phase, a migrating wave of regional cortical excitation, followed by depolarization and oligemia, results in visual, sensory, motor, or psychic phenomena, and clinically produces a wide variety of signs. In each instance, the signs evolve gradually, peak within minutes, and generally subside within minutes to hours, and may be followed by a typical migraine headache. So far, little evidence has been found regarding the cerebral origin of torticollis or vertigo, and of childhood periodic syndromes such as benign paroxysmal torticollis and benign paroxysmal vertigo. In both benign paroxysmal torticollis and benign paroxysmal vertigo, the pathogenic evidence derives mainly from molecular data. Giffin et al. reported on four patients with benign paroxysmal torticollis, two of whom were from a set of kinfolk with familial hemiplegic migraine with ataxia and a CACNA1A mutation [13]. The clinical course reflecting the changing, age-specific phenotypes associated with CACNA1A dysfunction (i.e., benign paroxysmal torticollis, benign paroxysmal vertigo, and familial hemiplegic migraine) was suggested by other authors [10,15,26,65]. Cuenca-León et al. screened eight Spanish patients with benign paroxysmal torticollis and benign paroxysmal vertigo for mutations in the three genes that were implicated in familial hemiplegic migraine: CACNA1A (familial hemiplegic migraine 1), ATP1A2 (familial hemiplegic migraine 2), and SCN1A (familial hemiplegic migraine 3) [66]. In a patient presenting the age-specific sequential phenotypes of benign paroxysmal torticollis, benign paroxysmal vertigo, and familial hemiplegic migraine, a novel CACNA1A polymorphism was identified. This is the first description of a specific nonsynonymous base change in a patient affected with a childhood periodic syndrome. The patient manifested the p.Tyr1245Cys polymorphism in the CACNA1A gene [66].

Thus some childhood periodic syndromes can be viewed as ionic channel disorders, which may explain their paroxysmal features in the absence of any structural changes. Some features of benign paroxysmal torticollis, such as its episodic nature, trigger factors, family association with migraine, and lack of anatomic lesions, would argue in favor of classifying it among such “channel pathologies.” The CACNA1A gene is expressed throughout the nervous system, and particularly in the cerebellum and at the neuromuscular junction. It encodes the pore-forming subunit of the main transmembrane neuronal (P/Q type) voltage-gated calcium channel.

The causes of abdominal migraine and cyclic vomiting syndrome remain unclear, but other pathogenic lines may be implicated. Recent hypotheses focused on autonomic instability as a primary pathogenic factor. Other proposed etiologies include disturbances in the hypothalamic-pituitary-adrenal axis, a mitochondrial disorder, and an abnormality in ion channels. Both the gut and the nervous system are derived from the same embryologic tissues, and the enteric nervous system and central nervous system exert direct effects on each other [67]. According to one proposed mechanism, stress contributes to increased arousal in the central nervous system, releasing neuropeptides and neurotransmitters that, in turn, lead to dysregulation of the gastrointestinal system. Although many individuals may experience some type of abdominal distress under stressful situations, those with recurrent abdominal pain may react to the stress differently, or may have maladaptive coping mechanisms [68].

The pathophysiology of cyclic vomiting syndrome has received more attention. Despite an incomplete understanding of its mechanisms, the pathophysiologic evidence points toward cyclic vomiting syndrome as a brain-gut disorder involving neuroendocrine pathways in genetically predisposed individuals [52,69]. According to an emerging consensus, cyclic vomiting syndrome involves dysregulated central neural pathways and neuroendocrine mediators involved in the afferent and efferent brain-gut pathways of nausea and vomiting [70]. Evidence from different lines of investigation indicates an important role of altered brain responses to visceral and emotional stimuli. Evidence has accumulated to suggest additional pathogenic roles for autonomic, gastrointestinal, central neuroendocrine, and mitochondrial metabolic factors. Common triggering stressors (e.g., psychologic or infectious) would initiate the vomiting cascade in patients with specific susceptibility factors (e.g., a family history of migraines, and
autonomic and gastrointestinal dysfunction, or energy deficits attributable to mitochondrial dysfunction). The corticotropin-releasing factor signaling system would thus be activated by stressors, and would play an important role in mediating autonomic alterations that affect gut motility [69,71]. The autonomic nervous system would play a prominent role, possibly via a sympathetic autonomic imbalance that may render patients more susceptible to an over-response to central emetic signals. Cellular energy deficits resulting from mitochondrial dysfunction may contribute to the autonomic dysfunction of cyclic vomiting syndrome that may be present in patients with cyclic vomiting syndrome. Recent studies characterized heteroplasmic mutations and cyclic vomiting syndrome and migraine-associated homoplasmic (i.e., one species of mitochondrial DNA present in the sample) polymorphisms in the small (1 kDa) mitochondrial DNA control region of a subset of children with cyclic vomiting syndrome [60,61].

### Conclusion

The clinical features and prevalence of the periodic syndromes of childhood are well-documented (Table 5). Nevertheless, they are probably under-recognized. It is worth emphasizing that practitioners should be aware of these benign events to ensure the correct diagnostic approach, sparing the child and family any needless anxiety or costly and sometimes invasive diagnostic procedures. The diagnosis relies on a careful semilologic analysis, mainly based on a parental description of manifestations. The family should be informed of the favorable prognosis. Finally, the periodic syndromes of childhood pose interesting questions about the varying phenotypic expressions of channelopathies at different stages of development, and may help unravel new neurobiologic mechanisms underlying migraine, ultimately leading to new therapeutic avenues.

### Table 5. Overview of childhood periodic syndromes

<table>
<thead>
<tr>
<th>Periodic Syndrome</th>
<th>Prevalence</th>
<th>Sex</th>
<th>Mean Age of Onset (Extremes)</th>
<th>Signs</th>
<th>Duration of Episodes</th>
<th>Age at Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign paroxysmal torticollis</td>
<td>Unknown</td>
<td>7 F/3 M</td>
<td>5 mo (0.25-30 mo)</td>
<td>Torticollis Dystonia</td>
<td>4.5 days (&lt;1-30 days)</td>
<td>3 yr (3 mo-5 yr)</td>
</tr>
<tr>
<td>Benign paroxysmal vertigo</td>
<td>2-2.6%</td>
<td>5 F/5 M</td>
<td>3 y (5 mo to 8 yr)</td>
<td>Vertigo Axatia</td>
<td>10 mo (a few seconds to 72 hr)</td>
<td>5 yr (2-16 yr)</td>
</tr>
<tr>
<td>Abdominal migraine</td>
<td>2.4-4.1%</td>
<td>F &gt; M</td>
<td>7 yr (infancy to adulthood)</td>
<td>Abdominal pain Pallor</td>
<td>4 hr (1-72 hr)</td>
<td>Adolescence to adulthood</td>
</tr>
<tr>
<td>Cyclic vomiting syndrome</td>
<td>0.04-1.9%</td>
<td>6 F/4 M</td>
<td>5 yr (6 days to 73 yr)</td>
<td>Vomiting Nausea</td>
<td>24 hr (2 hr to 10 days)</td>
<td>10 yr (may persist in adulthood)</td>
</tr>
</tbody>
</table>

Abbreviations:
- F = Female
- hr = Hours
- M = Male
- mo = Months
- yr = Years

References