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Episodic Syndromes that may be associated with migraine: a.k.a. “the childhood periodic syndromes”

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Abstract

Previously called “childhood periodic syndromes that are commonly precursors of migraine” in ICHD-II, these disorders were renamed “episodic syndromes that may be associated with migraine” in ICHD-III beta. The specific disorders reviewed in this article include: benign paroxysmal torticollis, benign paroxysmal vertigo, abdominal migraine and cyclical vomiting syndrome, as well as infantile colic which was recently added under the appendix section in ICHD-III beta.

Keywords

pediatric migraine; abdominal migraine; cyclic vomiting syndrome; infant colic; benign paroxysmal torticollis; benign paroxysmal vertigo

Introduction

Recognizing and understanding childhood periodic syndromes is important for several reasons. First, children with these disorders often undergo extensive and sometimes invasive medical testing. Recognizing their disorders as migrainous could spare them such testing. Appropriate treatment for these disorders of course first requires a correct diagnosis. Hearing about a history of a periodic syndrome might help a clinician to diagnose migraine headache in a child or adolescent down the line(1). Lastly, while migraine is clearly a largely genetic disorder, except in the case of the rare subform of familial hemiplegic migraine(2) it has been difficult to tease out the specific genes involved. This may be because the population of all migraineurs is heterogeneous, with different clinical phenotypes. More detailed clinical phenotyping that divides migraineurs into more homogeneous subgroups may facilitate gene discovery—and recognizing and phenotyping migraineurs by presence or absence of these childhood periodic syndromes is one way to improve clinical phenotyping.

In ICHD-II, the migrainous disorders of early childhood were referred to as “Childhood periodic syndromes that are commonly precursors of migraine”(3) or, colloquially, “childhood periodic syndromes”. In the ICHD-III beta version released in 2013, the terminology was changed to “episodic syndromes that may be associated with migraine”(4), partially in recognition that some of these disorders can affect adults. Benign paroxysmal

torticollis was moved from the appendix section into the main body of the document, and infant colic was added as a new disorder in the appendix section of ICHD-III beta. Cyclical vomiting syndrome and abdominal migraine were brought under a new umbrella term "recurrent gastrointestinal disturbance". For brevity, the term "childhood periodic syndromes" will still be used in this review.

This review covers the childhood periodic syndromes in the order of age that they typically occur in childhood: infant colic affects young babies, benign paroxysmal torticollis older infants, benign paroxysmal torticollis typically affects preschool aged children, and abdominal migraine and cyclical vomiting typically school aged children around six or seven years of age. Some children will evolve from one periodic syndrome into another with age(5-7). The latter two disorders have also been reported to have onset in adults, and benign paroxysmal vertigo can occasionally persist into adulthood(5). An important feature for all of these disorders is that between attacks the patients are healthy and have normal neurologic examinations.

Infant Colic

Infant colic, or excessive crying in an otherwise healthy and well-fed infant, occurs in 5-19% of infants(8, 9). Infant crying peaks at 5-6 weeks of life (corrected for gestational age at birth), and declines by 3-4 months of age(10, 11). Colic is an amplified version of this developmental crying pattern. The diagnostic criteria in the ICHD-III beta appendix are adapted from Wessel's criteria for colic, which are often used in pediatrics: crying for at least 3 hours a day, at least 3 days a week, for at least 3 weeks(4, 12). While the term "colic" implies abdominal discomfort as the etiology of the infant's distress, evidence for this localization is limited. Several trials of gastrointestinal oriented therapies have been negative(13-15). In addition, colicky infants typically do the bulk of their crying in the late afternoon and evening hours(10, 11), while feeding in young infants happens around the clock. It is important that we ultimately determine the cause of infant colic, as inconsolable and excessive crying leads to caregiver frustration and is associated with shaken baby syndrome, a form of child abuse with potential for significant neurologic morbidity and mortality(10, 16-18) . One percent of parents of one-month olds admit to having shaken their baby at least once to try to stop crying, and 2.2% have tried either shaking, slapping or smothering. By age six months, 5.6% have tried one of these dangerous techniques(19).

An association between infant colic and migraine has been reported in several retrospective case-control studies(20-22). In a cross-sectional study, mothers with migraine were more than twice as likely to have an infant with colic, pointing to the possible genetic relationship between infant colic and migraine(23). A recent meta-analysis found the odds of migraine were increased if there was a history of infant colic (OR 5.6 (95% CI 3.3-9.5))(24). A recent prospective cohort study done in Finland found that infant colic was associated with increased risk of migraine without aura by age 18 (RR 2.7 (95% CI 1.5-4.7)), but not migraine with aura(25), again highlighting the possibilities that certain genes lead to specific phenotypes of migraine.

Even if infant colic is in fact a migrainous disorder, it is still not known exactly why the babies cry. It may be that they are experiencing headaches, or perhaps abdominal pain

analogous to abdominal migraine. It is also possible that these infants have increased sensitivity to stimuli, just a migraineurs do, and that they express that increased sensitivity through excessive crying. With rapid brain development, neonates' visual perceptual ability increases significantly during the first few weeks of life(26). This could explain why colic does not begin until about two weeks of life, even though babies are feeding and interacting from birth onwards. There may also be a role for circadian biology in colic, as there is in migraine. Age three months is when the infant's endogenous melatonin secretion takes on a circadian rhythm that allows for nighttime sleep consolidation(27-29). Rhythmic melatonin secretion, either in itself or mediated by the ability to sleep through the night, could explain why colic resolves around age 3 months(30). Particularly in young children, sleep can help terminate a migraine attack(31).

Additional prospective cohort studies are needed to determine the natural history of children with infant colic—specifically whether they are more likely to go on to develop other childhood periodic syndromes, and whether they are more likely to have earlier onset of migraine headaches or a more severe form of the disorder. Treatment studies of infant colic are needed to see whether principles of managing migraine in children can be used to soothe colicky babies. We know that during a migraine attack children want to climb in bed and pull the covers over their heads and be in a dark, quiet room. A behavioral intervention wherein caregivers are trained to decrease stimulation when colicky crying starts—turn off the lights, quiet the musical toy—could potentially help babies, and in turn help frustrated caregivers, to remain calm. There is in fact a small study suggesting that such a strategy may be effective(32). Given how much additional evidence has accumulated about the relationship between infant colic and migraine since the ICHD-III beta version was released, it would seem sensible to bring it into the main document of the final 3rd edition(33).

Benign Paroxysmal Torticollis of infancy

The hallmark of this disorder is periodic, stereotyped bouts of torticollis during infancy(4). Onset is typically around five or six months of age(34). Attack duration can be on the order of minutes but typically last hours to days, and usually occur at regular intervals (e.g. monthly)(4, 35). The disorder typically begins to improve by age two and typically resolves by age three or four(34). There may be associated irritability, drowsiness, pallor, vomiting, ataxia, or tortipelvis(34, 35). Motor delay has been reported in some cases, and may improve as the disorder improves(34, 35). Often there is a family history of migraine. In some cases the infants have one of the CACNA1A gene mutations that have been associated with familial hemiplegic migraine(7, 36, 37). The disorder may be underdiagnosed as one study found that only 2.4% of pediatricians were aware of benign paroxysmal torticollis, however it also seems to be the rarest of the periodic syndromes(35, 38). Diagnostic yield of brain MRI and EEG are quite low(34). Treatment of benign paroxysmal torticollis is not well studied.

Benign Paroxysmal Vertigo of Childhood

Children with this disorder experience recurrent attacks of vertigo that seem to come out of the blue and last seconds to hours(4, 5), with the most common duration being less than five minutes(39). There can be accompanying nystagmus, ataxia, nausea/vomiting or pallor, and

the child may appear scared(4, 39). Headache can also accompany an attack(5, 6, 39). To formally meet ICHD-III beta criteria there needs to be normal audiometric and vestibular functions between attacks, but the requirement for a normal EEG found in ICHD-II(3) has been removed. However in cases where it is not clear that alteration of mental status is absent, obtaining an EEG is probably still worthwhile. As young children may have difficulty articulating vertigo, a parent's observation of episodic periods of unsteadiness is sufficient to infer vertigo in young children(4). This is analogous to how sensitivity to light and sound can be inferred from behavior in young children with migraine headache.

Typical age of onset is between two and five years of age(5, 39, 40). Some patients outgrow the disorder, typically around age 5-6 years(5, 40), however for others attacks can persist into adolescence or young adulthood(5). In one series that had long-term follow-up, a family history of migraine was seen in 70% and a third went on to have migraine as adults, which was higher than would be expected in the general population(40). In another small series with long term follow-up 69% had migraine(5). Timing of migraine onset is not well studied, but in one series 20% of children with BPV had developed migrainous headaches by age 7.5 years (median), which is higher than the population prevalence for age(39). Those cases that went on to develop migraine as adults had experienced benign paroxysmal vertigo in childhood for longer than those that did not (mean 3.01 years vs. 1.9 years, p=0.01)(40). It is possible that a genetic distinction differentiates those who have an age-sensitive time-limited disorder from those with a more chronic course. A mutation in the CACNA1A gene has been reported in a patient who first had benign paroxysmal torticollis, then benign paroxysmal vertigo, then hemiplegic migraine(7).

Cyclic Vomiting Syndrome

Children with cyclic vomiting syndrome (CVS) experience stereotyped episodes of frequent vomiting. The episodes are typically stereotyped for a particular individual and often occur at predictable intervals(4). By ICHD-III beta criteria, the vomiting must be at least four times per hour, though in ICHD-II it was required to be at least four times per hour for at least one hour during the episode, which seems to be a more reasonable criterion(3, 4). Children with cyclic vomiting syndrome are well between attacks.

CVS has also been reported to occur in adults. In children, mean age at onset is 5.2 years, whereas for adults it is 25.4 years. Attack frequency is about once a month on average and attack duration is typically several days. A personal or family history of migraine headache is common(41).

The differential diagnosis for cyclic vomiting syndrome is broad. Gastrointestinal pathology should be ruled out via consultation with a GI specialist and appropriate testing. Urologic disorders, such as ureteropelvic junction obstruction causing hydronephrosis, have been reported and can be diagnosed via abdominal ultrasound(42).

For the pediatric neurologist, a specialty-based differential to consider would include:

1. Autonomic seizures—In pre-adolescent children, Panyiotopoulous syndrome (peak age at onset 3-6 years) and Gastaut type epilepsy (peak age at onset 8-11 years)

would be diagnostic considerations(43), particularly if there is alteration of mental status.

2. Cannabinoid hyperemesis syndrome—This recently recognized disorder should be on the differential for an adolescent with cyclic vomiting. Frequent use of cannabis can lead to a periodic vomiting syndrome accompanied by a predilection for hot-water bathing(44).

3. Metabolic disorders—Serum and/or urine laboratory testing suggesting mitochondrial dysfunction has been reported in some children with CVS(45, 46). The mitochondrial DNA polymorphisms 16519C→T and 3010G→A have been associated with CVS in children(47). Rarely cyclic vomiting can be a presentation of disorders of fatty acid oxidation(48, 49).

Acute treatment consists of oral hydration or intravenous hydration if needed, as well as anti-emetics. Case series have suggested triptans are effective acute therapy in some patients. Given the significant vomiting, typically nasal spray or subcutaneous sumatriptan are used(50-53) however successful treatment with oral sumatriptan has also been reported(54). As the episodes are often quite debilitating, treatment with a migraine preventive may be worthwhile, though there are no randomized trials to guide agent selection. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend amitriptyline for children age 5 and up and cyproheptadine for younger children(55). There is some evidence that amitriptyline may be superior to propranolol for CVS prevention in children(56). The neurokinin-1 receptor antagonist aprepitant was found to be effective both as an acute therapy and as a preventive therapy (dosed twice weekly) for CVS in an open-label study(57).

Abdominal Migraine

This disorder usually has its onset in school-aged children and is characterized by bouts of abdominal pain lasting 2-72 hours in duration. Typically the pain is dull and often in the midline or poorly localized. The child may experience nausea, vomiting, anorexia, or pallor during the attacks(4). The children are well between attacks. Similarly to in cyclic vomiting syndrome, no gastrointestinal pathology is identifiable.

Abdominal migraine is likely the most common childhood periodic syndrome to present in a pediatric headache clinic; in one series accounting for 48.9%(38). The population prevalence has been estimated at 4.1% among 5-15 year olds(58). Mean age of onset is 7 years (SD 3.2). The mean attack frequency is 14 episodes per year, but with high variance (SD 22.4). Mean attack duration is 17 hours (SD 18.1), with a range of 1-72 hours(58).

There are case reports of successful treatment of acute attacks with nasal spray sumatriptan(59). As with cyclic vomiting syndrome, treatment with a migraine preventive may be worth consideration. A small case series suggests a course of IV dihydroergotamine may be helpful for refractory abdominal migraine in children(60). Randomized controlled trials of acute treatments for abdominal migraine are needed. If triptans are shown to be effective for acute treatment of abdominal migraine, it would be helpful to establish the positive predictive value of successful termination of an attack with a triptan in a child

presenting with recurrent migrainous abdominal pain. If the positive predictive value is high, perhaps children could be spared invasive testing such as upper endoscopy and colonoscopy.

Conclusions

The “episodic syndromes that may be associated with migraine” are a diverse group of disorders that predominantly occur in children but in some cases can also occur in adults. Recognition of these disorders is important for accurate diagnosis and treatment. Given the typically early childhood age of onset, the migrainous genetic underpinnings of these disorders would be expected to be strong. Detailed clinical phenotyping of children with these disorders could help in the search for specific migraine genes. There are not yet randomized clinical trials to guide treatment for these disorders. In some cases behavioral treatment, such as decreasing stimulation around a colicky infant, may be all that is needed and might be most appropriate in the youngest age group. In older children with frequent or disabling attacks, migraine preventives and acute treatments may be necessary and appropriate.

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Abbreviations

CVS	cyclic vomiting syndrome
BPT	benign paroxysmal torticollis
BPV	benign paroxysmal vertigo