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Title: Episodic Syndromes That May Be Associated with Migraine in Children

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Introduction:

Hello! My name is Stephanie Unrau, and I am a fourth-year medical student from the University of Alberta, in Edmonton, Canada. This podcast was developed with Dr. Thilinie Rajapakse, an Assistant Professor at the University of Alberta and Pediatric Neurologist specializing in Headache and Facial Pain at the Stollery Children's Hospital. In this podcast, we will discuss the five pediatric syndromes associated with a higher risk of developing migraine later in life, named the "Episodic Syndromes That May Be Associated with Migraine" as per the International Classification of Headache Disorders (ICHD-3), previously called "childhood periodic syndromes". Typical migraine headache is out of scope of this podcast.

By the end of the podcast, we want you to be able to:

- Describe the 4 main and 1 suggested type of episodic syndromes that may be associated with migraine
- Differentiate episodic syndromes that may be associated with migraine by presentation and diagnostic criteria
- Describe management and prognosis for these conditions

Let's start with a case!
You are a medical student on a pediatric neurology elective, consulted by the ER team to see Alice, a 5-year-old girl presenting with abdominal pain and vomiting. She is developmentally normal, otherwise healthy, and has had a negative GI and renal workup. What is your main differential and how can you narrow it down?

Episodic syndromes that may be associated with migraine are specific syndromes occurring primarily in childhood that are considered to be precursors to, or alternate types, of migraine[1]. The four of these syndromes in the ICHD-3 are: benign paroxysmal torticollis of infancy, benign paroxysmal vertigo of childhood, cyclic vomiting syndrome, and abdominal migraine; another that will likely be added in future is infantile

colic[7]. Although each syndrome is differentiated by diagnostic criteria as described in the ICHD as well as prevalence, age of onset, management, and prognosis, there are some unifying aspects of these syndromes as well. They are similar in that they are all **clinical diagnoses**, as there are no laboratory or imaging tests available or needed to rule in the diagnosis. Also, **between episodes**, children should have **complete resolution of symptoms**. Additionally, children with any of these syndromes should be otherwise **neurologically normal and have normal hearing**, and not demonstrate the above symptoms because of another disorder[2]. A child may experience only one of these syndromes, or have multiple within their lifetime. These syndromes all increase the risk that children will develop migraine later in life, and tend to occur in children with a family history of migraine. These disorders can also co-occur in children who already have typical migraine with or without aura[2]. Finally, they may also have other related conditions including motion sickness, or periodic sleep disorders (such as sleep talking, sleep walking, night terrors)[2] which will not be discussed further in this podcast. With these shared characteristics in mind, let's get to work on breaking down the different episodic syndromes that may be associated with migraine!

Infantile Colic

Infantile colic occurs in 5-19% infants, often with onset around 2 weeks old and resolution around 3 months old[6]. Wessel's Criteria for defining colic are 1) excessive crying in an otherwise healthy, developmentally normal, well-fed infant, where 2) excessive crying includes at least 3 hours a day, at least 3 days a week, for at least 3 weeks[6,7]. Pathophysiology is poorly understood and has historically been attributed to GI causes, however this relationship is in question as crying in colic is worse later in the day rather than dispersed throughout the day alongside feeding, and there is poor response to GI therapies[6]. Rather, it is possible that the excessive crying in colic is of neurologic origin, potentially resulting from headache, abdominal pain like abdominal migraine, or hypersensitivity to stimuli as experienced by older children with migraine[6]. In further support of a neurologic basis for colic, it is postulated that colic begins around two weeks when the rapidly developing brain becomes more acutely aware of visual stimuli, and resolves around 3 months due to the endocrine system establishing a circadian rhythm and the ability to sleep through the night, as sleep palliates and ends migraine in older children as well[6].

The association between infantile colic and migraine that would qualify it for inclusion as an episodic migraine syndrome has been demonstrated through an increasing number of studies[6,7]. A multicenter study in 2013 found an association between migraine (with or without aura) and colic, and suggested that colic is the earliest clinical manifestation of migraine, falling within the realm of the episodic syndromes[7,10]. Further evidence includes findings that mothers with migraine were more than two times more likely to have infants with colic; that an individual had an increased odds ratio (5.6) of developing migraine if they had colic as infant; that individuals with colic had an increased relative risk (2.7) of developing migraine without aura by 18 years old; and that children with

migraine are more likely to have personal history of colic, and to have a first degree family relative with migraine or history of colic[6,7].

This condition remits spontaneously around three months, with no effective medical management[9]. It is important to note that infants with colic are at elevated risk of shaken baby syndrome secondary to caregiver frustration[6]. Therefore, the mainstay of management is caregiver support, as well as conservative measures such as decreasing stimulus by sitting with the infant in a dark, quiet room (which also helps with migraine in older children)[6]. Other conservative measures that may be helpful include other soothing or feeding techniques[9]. It is also critical to support parents by reassuring them that colic is common, that their baby is not sick, that the colic is not their fault or evidence of the baby rejecting them, and acknowledging the difficult and negative emotions they may have from this experience[9]. It is especially important to encourage them to take breaks from the child when frustrated and to invite family supports in, so as to minimize the risk of shaken baby syndrome for the infant[9].

Benign Paroxysmal Torticollis of Infancy

Benign paroxysmal torticollis of infancy (BPTI) affects infants and young children, typically occurring at around 5-6 months of age and resolving spontaneously by 5 years of age[2,6]. The pathophysiology for BPTI, like for most of the episodic syndromes that may be associated with migraine, is largely unclear[1,7]. The ICHD-3 diagnostic criteria are "[recurrent attacks[1] in a young child, which consist of a tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days AND at least one of the following five associated symptoms or signs: pallor, irritability, malaise, vomiting and ataxia.][2]" The criteria further specify that the infant must have a normal neurological examination between attacks and no other disorder causing the observed symptoms, meaning that GERD, idiopathic torsional dystonia and complex partial seizure, and lesions in the posterior fossa and craniocervical junction must be ruled out before the diagnosis can be made.[2]

Does that all seem confusing, or not so bad? Maybe we can help by describing how to distinguish BPTI episodes a little more.[1,2,5,7] During head tilting events, the child's head can be returned to neutral, although there may be some resistance that can be gently overcome[2]. The events can be on alternating sides[5]. Events occur more frequently earlier on in life (2-8 months of age)[5], tend to occur monthly[2] overall, but can also occur at varying intervals[1]. In terms of duration, they usually last for hours, but can be minutes to days, appearing and ending suddenly[1]. The child typically remains alert and responsive during an event[1], although can also have drowsiness[5]. Ataxia is more common in older children[2]. In addition to the pallor, irritability, malaise, vomiting, and ataxia in the diagnostic criteria, children may also have certain typical migrainous features like photophobia and headache[7], but their EEG is usually normal (which helps to differentiate it from posterior fossa tumors or congenital muscular torticollis)[5]. To make this diagnosis, other disorders must be considered and ruled out (ie. EEG), and initial observations made in clinic or by parents should be validated by keeping

longitudinal symptom diaries[2], and bringing videos to the clinic[5]. As for management and prognosis, the episodes themselves resolve spontaneously, and BPTI events usually stop occurring by 5 years of age[1,7]; management has not been well studied[6]. These children may have no further complications, but the child is also at an elevated risk of developing other episodic syndromes that may be associated with migraine such as benign paroxysmal vertigo especially, and also migraine with aura (especially brainstem aura)[2].

Benign paroxysmal vertigo of childhood

Benign paroxysmal vertigo of childhood (BPVC) occurs a little later than BPTI, usually presenting around 2-4 years of age[1,7]. Like other episodic syndromes that may be associated with migraine, these children also often have a positive family history of migraine and motion sickness[1,7], but pathophysiology is poorly understood[4]. ICHD-3 criteria for diagnosis include “at least five attacks of vertigo occurring without warning, [which are] maximal [severity] at onset and [resolve] spontaneously after minutes to hours, WITHOUT loss of consciousness.[2]” They also must have “at least one of the following five associated symptoms or signs: nystagmus, ataxia, vomiting, pallor, or fearfulness.[2]” They must “have a normal neurological examination, audiometric and vestibular functions between attacks, and these symptoms cannot be attributed to another disorder.[2]” On your differential for children with these symptoms, you should exclude posterior fossa tumours, seizures, and vestibular disorders[2].
So, children with BPV of childhood are otherwise healthy, and have sudden episodes of vertigo that occur and resolve spontaneously[2]. To help you recognize an event (especially as vertigo can be difficult to recognize or describe in a toddler), here are some more details about how to distinguish an event[1,4,7]: in response to vertigo, children may display sudden unexplained fright, grasping for a support person, balance troubles, or fall. The vertigo is most intense immediately at onset, and although it can take hours to resolve, it usually does so in 1-5 minutes. Of the accompanying symptoms, nystagmus and vomiting are common whereas headache is atypical! Another pertinent negative is that they never lose consciousness in these episodes and usually there is no alteration in consciousness, either. These children can also have autonomic symptoms including dizziness, nausea, pallor, perspiration, photophobia, and phonophobia, similarly to migraine. Finally, as for timing of events, they may occur in clusters within a few hours; there may be daily events; or events as far apart as one every 3 months!
Like the other episodic syndromes, BPV of childhood resolves spontaneously[1,7]. This usually occurs around 5 years old for BPV (just like BPTI), and these patients often develop migraine later in life[1,7]. Additionally, they may also develop further childhood episodic syndromes, in particular cyclic vomiting or abdominal migraine.

Cyclic Vomiting Syndrome

Cyclic vomiting syndrome, or CVS, occurs in 1.9-2.3% of children, with an average age of onset of 5.3 years of age. It is highly associated with a maternal history of migraine in pediatric populations[3], and unlike most of the other episodic syndromes, there is an

adult-onset CVS as well. Another difference from some of the syndromes we have looked at so far is that the pathophysiology is a bit better understood[3,7]: CVS is theorized to be a "brain-gut disorder", involving both neuroendocrine pathways and genetic predisposition. While the most consistent association is between CVS and migraine, CVS has also been linked to mitochondrial dysfunction, autonomic dysfunction, HPA-axis hyperreactivity, rapid gastric emptying or gastroparesis, estrogen sensitivity, chronic cannabis use (from studies in adults), and food sensitivity[3].

CVS diagnosis based on ICHD-3 criteria includes "at least five attacks of intense nausea and vomiting, [that are] stereotypical in the individual patient and [recur] with predictable periodicity. Attacks are also characterized by all of the following: 1) nausea and vomiting occur at least four times per hour, 2) attacks last for ≥1 hour, up to 10 days, and 3) attacks occur ≥1 week apart.[2]" The child must have complete freedom from symptoms between attacks (although may develop coalescent CVS later), and the symptoms must not be attributable to another diagnosis[2]. Attacks in CVS often have a stereotypical prodromal period, commonly around 1.5 hours consisting of dramatic worsening of autonomic symptoms, including decreased muscle tone, pallor, lethargy, apathy; an emetic period lasting around 24 hours that can be bilious or non-bilious vomiting with headache, pallor, photo/phonophobia and abdominal pain; and a recovery phase where the nausea fades and their appetite returns as they settle back to baseline[7]. CVS episodes often begin in the early morning, between 2-7 am[3]. Half of patients have attacks every 2-4 weeks, but overall frequency of episodes is 12 per year[3,7,11]. 75% of patients can identify triggers, often excitement or infectious causes[3,7]. 47% of children with CVS also have co-morbid anxiety, which was found to have a larger negative impact on their quality of life than more severe CVS symptoms themselves[3]. All patients with CVS but especially teenage females are also susceptible to developing coalescent CVS, meaning chronic daily nausea between actual vomiting episodes[3]. Further, adolescents with CVS commonly develop postural orthostatic tachycardia syndrome (POTS), potentially due to altered elevated sympathetic and normal to decreased parasympathetic tone even at baseline[3]. Disorders on the differential that need to be ruled out from a pediatric neurology perspective include cannabinoid hyperemesis syndrome, autonomic seizures (especially with alteration in mental status), and metabolic disorders[6].

Prevention and management of vomiting episodes are very important because of the electrolytic disturbances particular to this episodic syndrome. On the prevention side, lifestyle interventions include regular and adequate sleep, exercise, fluids; avoidance of fasting and known triggers; and managing the psychiatric comorbidities such as anxiety[3]. Prophylactic medication should also be used if vomiting attacks occur more than once a month, last more than 24 hours at a time, or cause the child to miss significant school[3]. If any of these conditions are met, the 1st line medication for children under 5 years old is cyproheptadine, whereas children over 5 years old should

receive amitriptyline[3]. If these agents are ineffective, 2nd line prophylaxis include aprepitant or propanolol[3]. Once a cyclic vomiting episode has begun, an abortive medication such as sumatriptan can be given during the prodromal phase or within one hour of onset of the emetic phase, or else aprepitant if it can be given during the prodrome, at least 30 minutes prior to the emetic phase [3]. As a reminder, the prodrome in CVS tends to be similar every time, consisting of around an hour and a half of dramatic autonomic symptoms, such as decreased muscle tone, pallor, lethargy, and apathy in the child. If this window is missed, the child may require supportive care in hospital including IV fluids, anti-emetics, sedatives, and NSAIDs like ketorolac for abdominal pain[3]. The prognosis for CVS is usually spontaneous resolution in preteen (around 10 years old) or early teenage years, although it is possible to have CVS into adulthood. 75% of children with CVS go on to develop migraine by 18 years old, and they may also have an intermediary abdominal migraine phase[3]- the final episodic syndrome for our discussion.

ABDOMINAL MIGRAINE

Abdominal migraine occurs in 2-4% of children, and 4-15% of children with chronic periodic abdominal pain[1]. It presents between the ages of 2-10 years old, with peak prevalence at 10 years old[1]. Pathophysiology is uncertain, however 60% have family history of migraine so a genetic component is suspected, as well as CNS or endocrine imbalance, or ion channel disorders. This is again a diagnosis of exclusion, with particular traits to help separate it from other presentations of abdominal pain as this is a very common pediatric complaint. The ICHD-3 diagnostic criteria for abdominal migraine include at least five attacks of abdominal pain, where the “pain has at least two of the following three characteristics: 1) [it is] midline location, periumbilical or poorly localized; 2) [it has] a dull or “just sore” quality; and 3) [it is] of moderate or severe intensity” or interferes with daily life. Attacks must also have at least two of the following four associated symptoms or signs: 1) anorexia 2) nausea, 3) vomiting, and 4) pallor to meet criteria. Further, the “attacks last 2-72 hours when untreated or unsuccessfully treated,” and as with the other episodic syndromes, the child must have complete freedom from symptoms between attacks and be otherwise healthy[1], with no other disorder causing the attacks[2]. It is especially important to rule out GI or renal causes on history, exam, and investigations prior to making this diagnosis. Note that if the vomiting accompanying the abdominal pain is protracted, CVS should be considered over abdominal migraine.

Further qualities to look for on clinical presentation include similar triggers to typical migraine, including stress, physical exhaustion, and motion sickness- although triggers are not always identifiable[1]. Abdominal migraine can have aura as well, including visual disturbances, flashing lights, numbness, tingling, dysarthria, and muscle weakness[7]. Photo and phonophobia are uncommon[1,] and concurrent headache may be missed as the abdominal pain is much worse[1,2] . Although the symptoms of abdominal migraine do not occur during a typical migraine, if headache is present then migraine should be considered as a diagnosis[2]. Very important pertinent negatives for abdominal migraine

also include lack of fever or diarrhea[2], as these do not occur during abdominal migraine episodes[2].

As for management and prognosis, most abdominal migraine stops by early adolescence, although it is possible to persist into adulthood[1]. Around 70% of patients with abdominal migraine develop typical migraine later in life[1,2]. Management includes removing triggers via lifestyle interventions like getting adequate sleep and hydration, while avoiding amine/xanthine exposure (like in processed meats) and dealing with stress[1]. Abortive therapies such as ibuprofen and tylenol may be helpful if given early on[1]. Supportive therapies are limited to antiemetics for associated nausea and vomiting as needed, preferably given rectally to improve efficacy[1]. If attacks are frequent, daily prophylactic therapies such as cyproheptadine, propranolol, or pizotifen may be used[1].

Okay, so now that we've gone through the 4-5 episodic syndromes that may be associated with migraine in detail, let's get some practice differentiating them in our case.

You ask Alice if she is feeling better after the emergency doctor gave her fluids through her IV and some analgesic medicine, and she replies that she is feeling a bit better, as before "her tummy was hurting so bad aaaaaall over". Her mother confirms that she often has periods of dull, diffuse abdominal pain lasting for a few hours in the early mornings, a few times a month, ever since she started going to daycare. Alice looks very white during these episodes. Although Alice has gotten colds and "tummy bugs" a few times since starting to play with the other kids, her mom reports that it has been months since the last diarrhea or runny nose, while the tummy aches have continued. Her family doc has suggested increasing fibre, maintaining hydration, and keeping a diary to see if the tummy aches only occur on days that Alice is away from her mom, but it doesn't seem to have made any difference. The only trigger for Alice's tummy aches seems to be eating junk food, like hot dogs on picnics, but the tummy aches do occur independently of this as well. Both Alice's mother and maternal grandmother experience migraine. Alice does sometimes get nauseous in cars.

Any other questions?

If you said we still need to inquire about the vomiting, you are right!

You ask for more details about the triggers, timing, and frequency of the emesis. Alice's mom replies that she throws up when she gets her abdominal pain frequently. She will throw up 10 times or so in two hours, and then recover on her own. This seems to happen every 3 weeks, for the last 2 years. When asked about any symptoms before she starts vomiting, her mom replies that it's hard to say as the episodes start so early in the morning. However, she has noticed that if Alice wakes up before an episode, she seems to remain drowsy and want to stay in bed. In between tummy pain-vomiting days, she is a normal, happy, healthy kid and does not even get headaches. She has

never gone to the hospital for these problems, until now. Her mom notes that she was a "colicky baby".

Alice's neurological exam is normal, and you note that she is a right-handed child who appears her age and has no apparent dysmorphic features. You confirm by looking on her chart that GI and renal causes have indeed been ruled out, and that she has no pre-existing medical comorbidities that would explain these symptoms.

What are the two episodic syndromes that you would suspect here, and which one will you suggest to your preceptor?

You suspect cyclic vomiting syndrome and abdominal migraine. Although the criteria for both are met, CVS gets preference because of the protracted vomiting. You discuss the case with your preceptor, and then go together to share the diagnosis of CVS with Alice and her mother. You explain that this can become abdominal migraine or resolve in adolescence, and that Alice is at increased risk of developing migraine by the age of 18. You also make a management plan together, including encouraging Alice's family to reassess and manage stressors in Alice's life, and ensuring appropriate hydration, rest, and hot dog avoidance. Alice's mom agrees to try cyproheptadine QHS to try to decrease pain and vomiting episodes. You also provide a prescription for sumatriptan, and counsel it to be given within the prodromal period or an hour of the emetic period beginning, and that Alice should be brought to hospital early for supportive management if she looks unwell. You agree to follow-up in 3 months to check that her prophylaxis is providing adequate management of this condition.

Well done!

Let's go over some take-home points:

1. Episodic syndromes that may be associated with migraine are clinical diagnoses that occur primarily in children who are well otherwise between episodes, that usually resolve spontaneously with age but predispose these children to a greater risk of developing migraine. Other causes of disease need to be ruled out and the child should be normal neurologically.
2. Benign Paroxysmal Torticollis of Infancy has episodes of tilting of the head with maintained alertness that occurs and resolves spontaneously and also includes at least one of pallor, irritability, malaise, vomiting, or ataxia.
3. Benign Paroxysmal Vertigo of Childhood occurs as sudden fearfulness or instability that is maximal at onset and usually resolves within 5 minutes, in a toddler or young child who maintains consciousness and may also have nystagmus, vomiting, pallor, or ataxia.
4. Cyclic Vomiting Syndrome usually occurs around 5 years old and resolves around 10 years old. It is composed of events with at least 4 episodes of vomiting

per hour for at least 1 hour up to 10 days, with at least 1 symptom-free week between episodes.
5. Abdominal Migraine commonly onsets around 10 years old and resolves around puberty or the early teenage years, and presents as moderate to severe achy pain either diffusely or periumbically, and is accompanied by at least 2 of anorexia, nausea, vomiting or pallor for a 2-72 hour period if untreated.
6. Infantile Colic is likely another episodic syndrome that may be associated with migraine, and can be recognized as an infant who is otherwise healthy and well fed but cries excessively for at least 3 hours a day, 3 days a week, for 3 weeks, typically between 2 weeks and 3 months old.
7. These can be frightening and disabling for young children and their families. Close follow up, reassurance and occasionally pharmacologic management can help manage these symptoms, with surveillance towards the likely development of migraine in the future.

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