

Before the Headache: Episodic Syndromes Associated With Migraine

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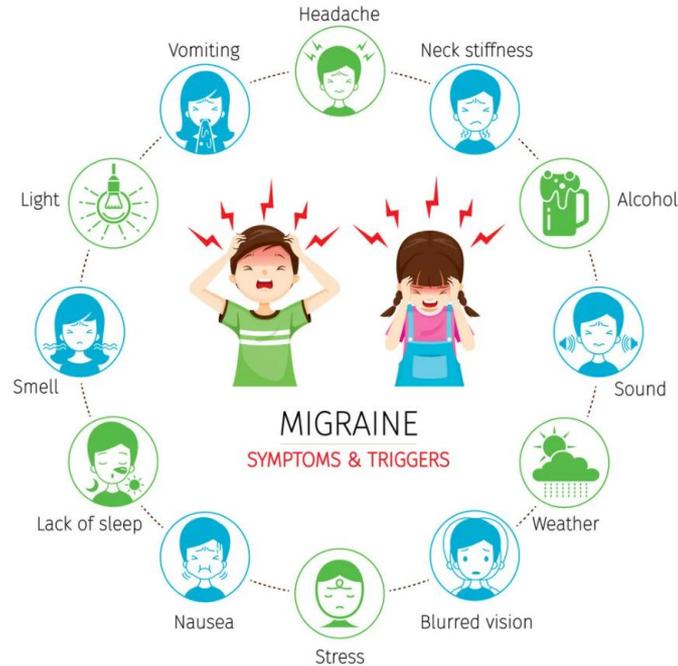


Disclosures

- Consultant: Theranica
- Contributing Author: Merck Manual



Migraine is **NOT** just a headache!



Objectives

- Review the evolution of migraine from childhood to adolescence
- Illustrate cases of episodic syndromes associated with migraine
- Discuss diagnostic criteria and management of episodic syndromes



Episodic Syndromes That Maybe Associated With Migraine

- Aka:
 - Childhood periodic syndromes
 - Migraine equivalents
 - Migraine precursors
- Group of periodic disorders in patients who have increased likelihood of developing migraine; or occurring in patients who also have migraine
- Represent early expression of migraine genes that later in life are expressed as “typical” migraine

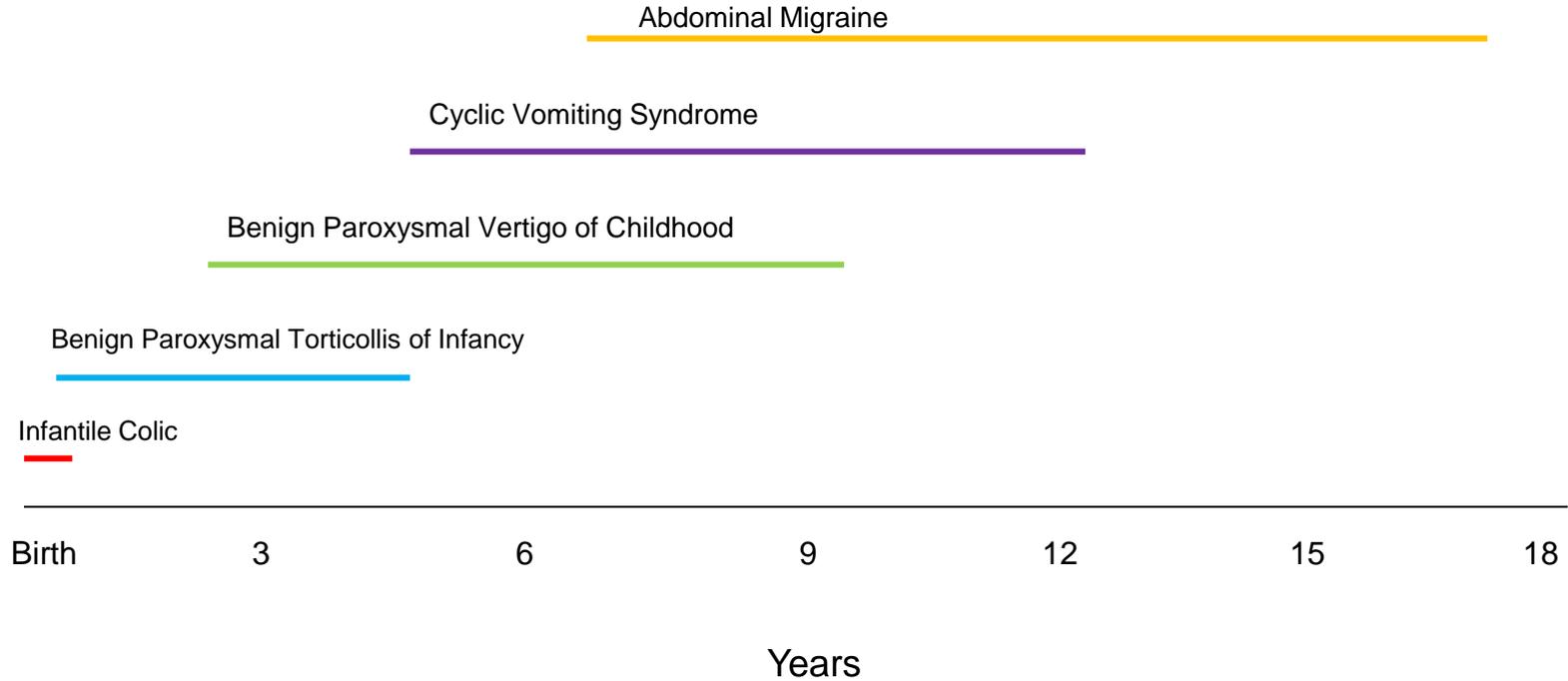


Common Key Clinical Features

- Periodic nature
- Normal neurologic examination between attacks
- Family history of migraine
- Clinical evolution to classic types of migraine
- Challenging to diagnose



Age-Related Expression of Episodic Syndromes Associated with Migraine



Case Vignette: The Colicky Baby

- 6 week old healthy baby with bouts of prolonged crying, usually in the evening, even when well fed.
- No other symptoms
- Bottle fed
- Birth history: Unremarkable
- Family History: Mother and maternal grandmother with migraine
- Exam: Normal
- Recommended: hypoallergenic formula; behavioral and environmental interventions; reassurance
- Follow-up at 3 months of age: Colic resolved



Infantile Colic



Presents with excessive, frequent crying in an otherwise healthy and well-fed baby

Prevalence: 5-19% of infants

Peaks: 6-8 weeks

Tapers down: 3 months

Bouts of crying (Wessel's criteria)

- ≥ 3 hours per day
- ≥ 3 days per week
- For ≥ 3 weeks



International Classification of Headache Disorders (ICHD)-3 Diagnostic Criteria

- A. Recurrent episodes of irritability, fussing or crying from birth to 4 months of age, fulfilling criterion B

- B. Both of the following:
 1. episodes last for ≥ 3 hours/day
 2. episodes occur on ≥ 3 days/week for ≥ 3 weeks

- C. Not attributed to another disorder.

Note: In particular, failure to thrive has been excluded.



Etiopathogenesis

- Remains uncertain
- Possible multiple etiologies
 - CNS involvement
 - Psychological/Behavioral
 - Gastrointestinal (e.g. milk allergy, poor gut motility)



Evidence for a Relationship Between Infant Colic and Migraine

- Finnish Study of 1267 infants followed from birth
- 13% of infants with colic
- 867 infants were followed until 18 years
- 16% had migraine and 22% had history of colic
- Infantile colic is associated with increased risk of migraine without aura- (RR 2.7, 95% CI 1.5-4.7)

Sillanpaa M, Saarinen M. Cephalalgia. 2015;35:1246-51



Evidence for a Relationship Between Infant Colic and Migraine

- Cross-Sectional Survey Study
- 154 infant-mother pairs
- 14% of infants with colic
- Maternal family of migraine increases likelihood of having a baby with infant colic by 2.6 fold (95% CI 1.2-5.5)

Gelfand AA, et al. Neurology.2012;79:1392-6



Evidence for a Relationship Between Infant Colic and Migraine

- Comparison of children with migraine (n=208) to healthy controls (n= 471)
- 72.6% of children with migraine and only 26.5% of matched controls had history of colic (OR 6.61 95% CI 4.4-10)

Romanello S, et al. JAMA. 2013; 309:1607-12



Evidence for a Relationship Between Infant Colic and Migraine

- 2015 meta-analysis
- 3 studies included in the final analysis
- 67% of migraineurs had a history of colic vs. 23% of those without migraine having colic
- Infant colic significantly increased association with migraine- (OR 5.6, 95% CI 3.3-9.5)

Gelfand AA. Cephalalgia.2015; 35:63-72



What Will Explain the Link Between Migraine and Infant Colic?



Migraine genes may make these infants more sensitive to stimuli



Crying is a manifestation of hypersensitivity



Influence of circadian biology



Possible involvement of calcitonin gene-related peptide (CGRP)



Management

- Reassure parents
- Non-pharmacologic management
 - Reduce certain types of stimulation
 - Modify parents' responsiveness
- Maternal hypoallergenic diet or hypoallergenic formula maybe considered
- Drug therapy is not recommended.



Key Points to the Primary Care Provider

- When seeing a colicky baby, ask if there is maternal family history of migraine
- Counsel pregnant women with migraine that they are more likely to have a colicky baby and reassure them that infantile colic is time-limited and will pass.



Case Vignette: The Baby with a Head Tilt

- One year old girl presents to neurology clinic for a second opinion
- At 6 months of age:
 - seen at ED for head tilt to the right associated with vomiting and irritability.
 - Conscious the whole time. +pallor
 - Lasted ~ 1-2 hours. At the ED, symptoms were already resolving and exam was normal. Labs were done and was sent home
- 2nd episode: 4 weeks later
 - Head tilt to the right with rotation of the neck , vomiting, pallor, irritability
 - Admitted. vEEG, brain MRI, urine drug screen, labs– normal
 - Symptoms resolved spontaneously after 4 hours
- Exam and developmental screening were normal
- Family history: mother with migraine without aura; maternal aunt with hemiplegic migraine
- After the second episode, she was clinically diagnosed to have seizure and family declined treatment
- In between attacks, patient was normal. 3rd episode occurred hence the consultation



Benign Paroxysmal Torticollis of Infancy (BPTI)

- Probably the rarest of the episodic syndromes
- Onset: usually 1st 6 months of infancy
- Mean age of onset of first attack: 6 months
- Recurrent episodes of painless head tilt (i.e. torticollis, cervical dystonia)
- Associated symptoms:
 - Irritability
 - Pallor
 - Nausea or Vomiting
 - Ataxia
- Onset is sudden; majority in the mornings
- Duration: hours to days; some last for few minutes
- Resolves spontaneously by 5 years of age

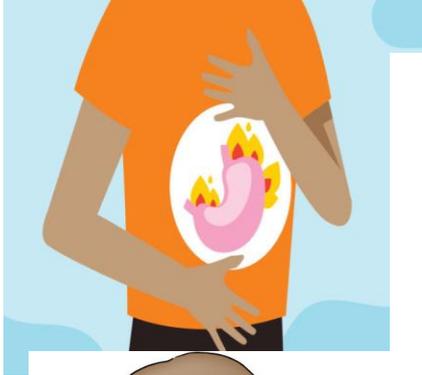


ICHD-3 Diagnostic Criteria

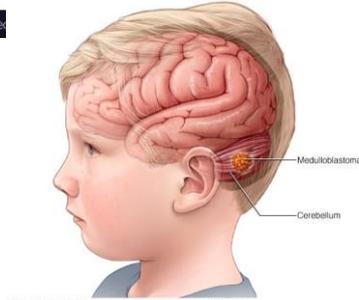
- A. Recurrent attacks in a young child, fulfilling criteria B and C
- B. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
- C. At least one of the following five associated symptoms or signs:
 - pallor
 - irritability
 - malaise
 - vomiting
 - Ataxia
- D. Normal neurological examination between attacks
- E. Not attributed to another disorder.



Differential Diagnosis



FOCAL



Gastroesophageal reflux

Idiopathic torsional dystonia

Focal seizure

Posterior fossa tumor or
craniocervical junction lesions



Akron Children's Hospital

Etiopathogenesis

- Remains uncertain
- Possible etiologies:
 - Underlying vestibular disorder (e.g. labyrinthitis)
 - Involvement of vestibulocerebellar connections
 - Immaturity of the brain
 - Channelopathy
 - Mutation in the CACNA1A gene (*Shin M, et al. J Child Neurol 2016; Vila-Pueyo M, et al. Eur J Paediatr Neurol. 2014; Roubertie A, et al. J Neurol. 2008; Griffin et al. Dev Med Child Neurol. 2002*)
 - PRRT2 mutation (*Dale RC, et al. Dev Med Child Neurol 2012*)



Evidence for an Association with Migraine

- 55% had family history of migraine (*Drigo P, et al. Brain Dev 2000*)
- Some cases of an association with genes associated with FHM (CACNA1A and PRRT2)
- Develop other episodic syndromes (*Drigo P, et al. Brain Dev 2000; Bermucci MC, et al. J Headache Pain 2015*)
- History of BPTI increases likelihood of having migraine with vertigo (*Teggi R, et al. Headache 2017*)

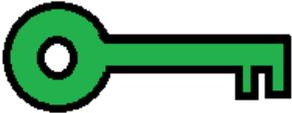
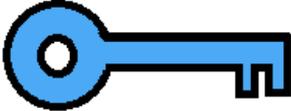
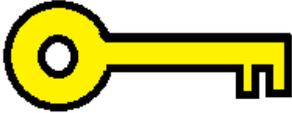


Management

- Limited information
- When infrequent and brief: reassure family
- When more frequent and severe:
 - Acute treatment:
 - consider NSAIDs; anti-emetics for older infants/toddlers
 - Preventive treatment:
 - Case reports of efficacy of Topiramate 2-4 mg/kg/day (Yaghini O, et al. Pediatrics 2016)
 - In my practice: Cyproheptadine (0.25- 0.5 mg/kg/day)
- Monitor development due to some reports of motor delay



Key Points for Primary Care Provider



Recognize symptoms of BPTI to avoid diagnostic delay and associated distress for the family

For patients with BPTI, screen for developmental delay and refer to services when necessary

Ask about family of hemiplegic migraine. If positive, consider referral to neurology or genetics for testing for CACNA1A mutation



Case Vignette: The Dizzy Child

- 3 year old healthy boy was playing when he suddenly stopped playing
 - Sudden became fearful
 - Grasp mother's hands
 - Off balanced and wobbly
 - Pale and cold sweats
 - Jiggly eyes
- Immediately brought to ED. En route (<5 minutes), symptoms resolved
- Exam normal
- Similar episode occurred 3 months later.
- Strong family history of migraine
- He has history of car sickness
- Brain MRI, EEG and ENT evaluation were normal



Benign Paroxysmal Vertigo



- Recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously, in otherwise healthy children
- Two peaks:
 - 2- 4 years
 - 7- 11 years
- Most common cause of episodic vertigo in children between 2 and 6 years
- 2017 systematic review: ~14% of children presenting with vertigo were diagnosed to have BPV (*Davitt M, et al. Pediatr Emerg Care 2017*)
- Most common cause of dizziness referred to ENT specialist



ICHD- 3 Diagnostic Criteria

- A. At least five attacks fulfilling criteria B and C
- B. Vertigo occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
- C. At least one of the following five associated symptoms or signs:
 - nystagmus
 - ataxia
 - vomiting
 - pallor
 - fearfulness
- D. Normal neurological examination and audiometric and vestibular functions between attacks
- E. Not attributed to another disorder.



Differential Diagnosis

- Posterior fossa tumor
- Seizures
- Vestibular disorders
- Infection- when clinical scenario is appropriate
- Ocular disorders
- Traumatic brain injury



Evidence for an Association with Migraine

- 70% with family history of migraine and 33% developed migraine as adults
(Batuecas-Caleterio a, et al. Eur J Paediatrc Neurology. 2013)
- ~20% developed migraine by age 7 *(Batu ED, et al. Eur J Paediatrc Neurology. 2015)*
- Maybe associated with likelihood of having migraine with vertigo in adulthood
- Possible early-onset variant of migraine with brainstem aura (aka basilar migraine)



Etiopathogenesis

- Unknown
- Possible theories:
 - Peripheral vestibular dysfunction
 - Central vestibular pathology



Management

Acute treatment– usually not practical due to brief duration

When attacks are very frequent

- Consider preventive therapy
- Use medications used for migraine prevention with known safety profiles in this age group
 - Cyproheptadine
 - Propranolol



Key Points for Primary Care Providers

- Ask about a family history of migraine. It may help diagnose BPV
- Refer to neurology if the child is having frequent attacks, or there is nystagmus or alteration of consciousness with attacks as epilepsy may need to be ruled out



Case Vignette: The Pukey Child

- A 5 year old girl presents to the clinic for recurrent vomiting
- Occurs every 8 weeks
- Wakes up vomiting between 2:00 and 4:00 am
- Throws up at least 6 times per hour
- Lasts 24 hours then she bounces back as if nothing happened
- Has been to ED in some of these episodes for hydration
- Associated symptoms: occasionally has abdominal pain.
- Examination: Normal
- No developmental regression
- Negative Brain MRI, EEG, metabolic work-up
- Family history: +sister with migraine and similar symptoms during childhood



Cyclic Vomiting Syndrome (CVS)

- Recurrent episodic attacks of intense nausea and vomiting
- Usually stereotypic
- With predictable timing of episodes.
- Associated symptoms:
 - Pallor
 - Lethargy
 - Abdominal pain
- Complete resolution of symptoms between attacks.



Demographics

- Described in all races and ethnicities; more often reported in children of Northern European ancestry
- Girls>boys
- Prevalence: 1.9 – 2.3% of children
- Incidence: 1.7 – 2.7%
- Second most common cause of recurrent vomiting in children after GERD
- Average age of onset: 4-7 years of age
- Some case reports of adult onset*
- Median age of resolution: 10 years



ICHD-3 Diagnostic Criteria

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



Differential Diagnosis

- GI pathology (e.g. malrotation with volvulus)
- Metabolic disorders (e.g. fatty acid oxidation disorder)
- Mitochondrial disorder
- Increased intracranial pressure
- Occipital lobe epilepsy (e.g. Panayiotopoulos syndrome)
- Munchausen-by-proxy syndrome
- In an adolescent or older patient, think Cannabinoid Hyperemesis Syndrome



Etiopathogenesis

- Uncertain
- Proposed theories:
 - Alteration of corticotropin-releasing factor and vasopressin release at the hypothalamic-pituitary level
 - Autonomic dysfunction
 - Disorder of mitochondrial metabolism



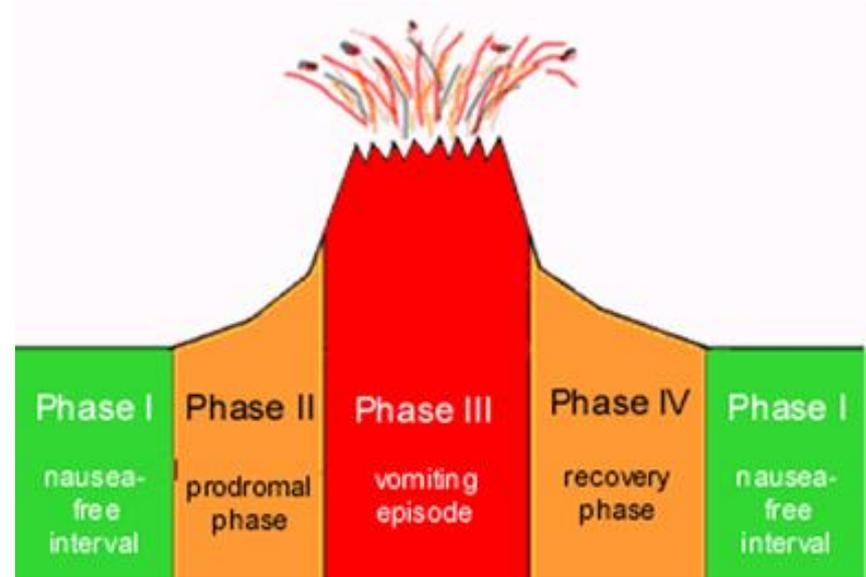
Evidence for Association with Migraine

- ~40% also had past history or present history of migraine (*Lee LYW, et al. Eur J Gastroenterol Hepatol 2012; Fitzpatrick E, et al. Arch Dis Child 2007*)
- Family history of migraine in up to 82% of patients
- Prediction analysis estimated that 75% would develop migraine by 18 years (*Li B and Misiewicz. Gastroenterol Clin North Am 2003*)



Four Phases of CVS

- 1) Interepisodic Phase
- 2) Prodromal Phase
 - Nausea
 - Pallor
 - Lethargy
 - Decreased muscle tone
- 3) Emetic Phase
 - Intense vomiting
 - Anorexia
 - Abdominal pain
 - Increased salivation
 - Photophobia and phonophobia
- 4) Recovery Phase



Triggers



- Over 75% have recognized triggers
- Lack of sleep
- Physical exhaustion
- Emotional excitement
- Food (i.e. cheese, chocolate, MSG)
- Trauma
- Psychological stress



Management

- Needs individually tailored regimen
- Identification and avoidance of triggers
- Behavioral self-management techniques



Acute Therapy

- Prodromal phase
 - Control the environment (dark and quiet room)
- Anti-emetic agents
 - Ondansetron
 - Promethazine
 - Combination with Diphenhydramine



Acute Therapy

- Emetic Phase
 - Supportive therapy
 - IV hydration
 - Anti-emetics
 - Sumatriptan IN or SC- effective in 54% of attacks



Preventive Therapy- Indications

- Acute therapy fails consistently
- Episodes are frequent
 - More than once per month
- Severe and disabling



Preventive Therapy

Recommendations from the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition

- ≤ 5 years
 - Cyproheptadine
 - Propranolol
- > 5 years
 - Amitriptyline
 - Propranolol
- Others:
 - Pizotifen
 - Erythromycin
 - L-Carnitine
 - CoQ10



Key Points for Primary Care Providers

01

Care coordination among multiple specialists will be needed to get a clear diagnosis of CVS

02

Once a diagnosis and treatment plan has been made, ensure that the family knows what to use as first line treatment and when IV hydration is needed.

03

Be cautious of CVS in a teenager and gain their trust in order for them to disclose cannabis use.



Case Vignette: The First Grader With Belly Pain

- 7 year old girl complains of abdominal pain since start of school year
- Character of pain: “just sore”
- Location: around the belly button
- Associated symptoms: nausea, anorexia, pallor. No headache. No constipation or diarrhea
- Duration: 2-4 hours
- Frequency: ~ once per week
- Past Medical History: unremarkable but mother reported she was a colicky baby
- Family History: Mother and maternal grandparents have migraine
- Examination: Normal
- She has seen GI and evaluation was normal



Abdominal Migraine

- Recurrent, acute onset, moderate to severe abdominal pain
- Dull or “just sore” in quality
- Midline, periumbilical or poorly localized
- Associated symptoms: nausea, anorexia, vomiting, pallor
- Duration: 2-72 hours when not treated
- Prevalence: 2.4 – 4.1%
- Mean age of onset: 7 years
- Peak of prevalence: 10 years



ICHD-3 Diagnostic Criteria

- A. At least five attacks of abdominal pain, fulfilling criteria B–D
- B. Pain has at least two of the following three characteristics:
 - 1. midline location, periumbilical or poorly localized
 - 2. dull or “just sore” quality
 - 3. moderate or severe intensity
- C. At least two of the following four associated symptoms or signs:
 - 1. anorexia
 - 2. nausea
 - 3. vomiting
 - 4. pallor
- D. Attacks last 2-72 hours when untreated or unsuccessfully treated
- E. Complete freedom from symptoms between attacks
- F. Not attributed to another disorder.



Etiopathogenesis

- Poorly understood
- Proposed Theories:
 - Brain-Gut connection
 - Natural progression of thalamic processing
 - Visceral hypersensitivity to distention in response to neurophysiologic abnormalities at the level of the gut, spinal cord and higher cortical systems
 - Possible evolution of CGRP expression pattern



Evidence for Association With Migraine

- May be preceded by prodromal signs
 - Behavior or mood change
 - Anorexia
- May be preceded by an aura
 - Visual disturbance
 - Flashing lights
 - Numbness or tingling sensation
 - Slurred speech
- Presence of triggers
 - Travel
 - Prolonged fasting
 - Irregular sleep habits
 - Stress
 - Dietary triggers
- 34-90% have history of migraine in a 1st degree relative
- Evolution to migraine headache (abdominal migraine at 7 years-> abdominal and head pain at 8-9 years -> migraine headaches alone by 10 years)



Management

- Non-pharmacologic treatment
 - Explanation and reassurance
 - Lifestyle changes and avoidance of triggers
 - Cognitive Behavioral Therapy
- Acute Treatment
 - Sumatriptan nasal spray
- Preventive Therapy:
 - Pizotifen (based on RCT)
 - Flunarizine
 - Cyproheptadine
 - Amitriptyline
 - Propranolol



Key Points of the Primary Care Provider



Abdominal migraine symptoms do not necessarily indicate a gastrointestinal tract pathology.



Abdominal migraine may be treated using medications used for migraine



Conclusion

- The phenotypes of migraine can be broad in the developing brain.
- Episodic syndromes may represent early life manifestations of migraine in a child or adolescent.
- Knowledge of these episodic syndromes may help clinicians clinch the diagnosis and choose appropriate treatment.



