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REVIEW

Pediatric abdominal migraine: current perspectives on a lesser known entity

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Background: Abdominal migraine (AM) is a common cause of chronic and recurrent abdominal pain in children. It is characterized by paroxysms of moderate to severe abdominal pain that is midline, periumbilical, or diffuse in location and accompanied by other symptoms including headache, anorexia, nausea, vomiting, or pallor. Despite the presence of comprehensive diagnostic criteria under Rome IV classification of functional gastrointestinal disorders (FGIDs) and International Classification of Headache Disorders, it continues to be an underdiagnosed entity.

Overview: The average age of diagnosis is 3–10 years with peak incidence at 7 years. Most of the patients have a personal or family history of migraine. Pathophysiology of the condition is believed to be similar to that of other FGIDs and cephalic migraine. It is also well recognized as a type of pediatric migraine variant. A careful history, thorough physical examination, and use of well-defined, symptom-based guidelines are needed to make a diagnosis. Selective or no testing is required to support a positive diagnosis. It resolves completely in most of the patients. However, these patients have a strong propensity to develop migraine later in life. Explanation and reassurance should be the first step once the diagnosis is made. Nonpharmacologic treatment options including avoidance of triggers, behavior therapy, and dietary modifications should be the initial line of management. Drug therapy should be considered only if symptoms are refractory to these primary interventions.

Conclusion: More research focused on pathophysiology and management of AM needs to be carried out to improve outcomes in affected children.

Keywords: children, abdominal pain, gastroenterology, headache

Introduction

Practice gap

Chronic and recurrent abdominal pain is a very distressing symptom that causes significant morbidity in affected children impairing their school performance and overall quality of life.[1–3] Chronic abdominal pain in childhood accounts for 2%–4% of office visits to primary care clinicians and 50% of referrals to pediatric gastroenterologists.[2] It also utilizes a lot of community health resources with frequent emergency room visits, hospitalizations, and expensive laboratory and imaging services. Abdominal migraine (AM) is one of the most common causes of functional abdominal pain in children and is included under the Rome IV classification of functional gastrointestinal disorders (FGIDs).[4] It is also currently well recognized as a type of pediatric migraine variant and has specific diagnostic criteria under the International Classification of Headache Disorders (ICHD) III.[5–7] Despite the presence of well-defined diagnostic criteria, AM

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is still a lesser known entity and is underdiagnosed by both general pediatricians and pediatric gastroenterologists.[8] More awareness about the essential clinical characteristics of the disease would improve diagnostic accuracy and guide clinicians in choosing the appropriate management for these patients. This would result in optimal utilization of health resources and also improve long-term outcomes in affected children.

Learning objective

The primary objective of this article is to highlight the current understanding and summarize the most recent advances in the pathogenesis, diagnosis, and management of AM in children. We have also outlined the differential diagnoses and clinical association of the condition with cephalic migraine, other pediatric migraine equivalents, and FGIDs.

Definition

AM is characterized by paroxysmal episodes of moderate to severe, poorly localized periumbilical, midline, or diffuse abdominal pain lasting ≥1 hour. Episodes are separated by weeks to months and there is a stereotypical pattern and symptoms in each patient. The pain is severe enough to interfere with normal daily activities. Abdominal pain is usually associated with other symptoms such as headache, pallor, anorexia, nausea, vomiting, and photophobia.[4–7] After appropriate medical evaluation, symptoms cannot be attributed to any other medical condition. Most often, there is a family history of migraine and it has a strong propensity to evolve into migraine headaches in adulthood.

Historical considerations

The term "abdominal migraine" was first used by Brams in 1922 to describe functional epigastralgia that occurs in patients at periodic intervals.[9] He also noted that there was a strong association of the condition with migraine. Most patients had migraine themselves or had a family history of migraine and also responded well to anti-migraine therapy. 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.[10] Russell and Symon in 1986 reviewed the clinical characteristics of 40 children with possible AM and also demonstrated the effectiveness of anti-migraine therapy in these patients.[11] They observed that symptoms continue to manifest as headaches or vomiting in adults.

In 1991, Axon et al raised a question "abdominal migraine: does it exist?" They concluded that even though well-defined diagnostic criteria are not available, AM is indeed the diagnosis in a subset of patients with recurrent chronic abdominal pain.[12] The relationship between recurrent abdominal pain and migraine headaches was demonstrated in multiple studies over the years.[13–16] In 1999, AM was included under the Rome II classification of FGID with well-defined guidelines. In 2001, Dignan et al also published a set of comprehensive guidelines for diagnosing AM.[17] The International Headache Society recognized AM as a pediatric migraine equivalent in 2004 and included it under the ICHD II classification (in Section 1.3, under childhood periodic syndromes that are precursors to migraine) and outlined clear diagnostic criteria.[5–7]

In 2013, ICHD III edition (beta version) was published and AM was categorized under "episodic syndromes that may be associated with migraine." Most recently, in May 2016, Rome IV classification of FGID was released and the diagnostic criteria for AM were revised.[4]

Epidemiology

Chronic abdominal pain occurs in 11%–15% of children and adolescents.[1,18,19] The overall prevalence of AM is ~1%–9%.[20–23] It is most commonly seen in children aged 4–15 years. The average age of diagnosis is 3–10 years with peak incidence at 7 years. Most of the studies have shown a higher prevalence in girls compared to boys, similar to other FGIDs and cephalic migraine.[24–26] A few studies have shown equal prevalence in girls and boys.[8,27]

In 2006, Carson et al conducted a retrospective chart review on children aged 1–21 years who were referred to an academic pediatric gastroenterology center with chief complaint of recurrent abdominal pain.[8] ICHD II criteria were used to identify patients with AM who met the diagnostic criteria. Of the 548 patients who met the inclusion criteria, 4.4% (20) met the ICHD II criteria for AM. Another 50 (11%) had documentation lasting at least one criterion, but were otherwise consistent with AM (probable AM). Thus, AM represented 4%–15% of children with chronic, idiopathic, recurrent abdominal pain. They also pointed out the "transAtlantic dissociation" of AM. During the assessment period from January 2006 to December 2007, none of the children in the Pediatric Gastroenterology Clinic received a diagnosis of AM. Most of the literature pertaining to AM comes from Europe and UK and there are very little data from the USA. They hypothesized that there is inadequate awareness about AM among clinicians in USA leading to underdiagnosis of the condition.

A 2008 study compared the prevalence of various FGIDs in children with chronic, idiopathic abdominal pain using

Rome II and Rome III criteria.[28] The frequency of diagnosis of AM in patients with chronic abdominal pain increased from 5% to 23% when using Rome III criteria. This proves that Rome III criteria had a more positive predictive value (100%) and a low negative predictive value (7.7%). This might have led to incorrect diagnosis of other functional abdominal pain disorders (FAPDs) as AM.

There have been no new studies reported so far that looked at the prevalence and other epidemiological characteristics of AM based on Rome IV criteria released in 2016.

Pathophysiology

There are several hypotheses that have been postulated to explain the pathophysiology of AM but none of them have been definitively confirmed.

Visceral hyperalgesia hypothesis

Visceral hypersensitivity is the most definitive and unifying theory explaining the pathophysiology of all FGIDs.[29] This theory is based on the strong association between the enteric nervous system and central nervous system (CNS) and their common embryonic origin. Patients with FGIDs have a low threshold for nociceptive stimuli. A variety of ill-defined factors including genetic, environmental, psychosocial (early stressors in life) etc predispose an individual to visceral hyperalgesia. Postulated mechanisms for visceral hyperalgesia include sensitization of primary sensory neurons and central spinal neurons, altered descending inhibitory control, and impaired stress response. This in turn causes alteration of bowel–gut axis and causes abnormal secretion of excitatory neurotransmitters such as serotonin. Serotonin plays a key role in the regulation of gastrointestinal (GI) motility, secretion, and sensation. The bidirectional communication between the brain–gut neurons through various neural and hormonal circuits may lead to changes in the CNS and cause other associated symptoms such as headache. Stimulation of the autonomic nervous system and sympathetic hyperactivity may account for symptoms such as pallor. Novel imaging techniques such as functional magnetic resonance imaging have shown defective visceral pain processing pathways in patients with FGID.

Although, the theory of visceral hyperalgesia has not been specifically proven in patients with AM, it is the most evidence-based explanation for all FGIDs.

Altered gut motility hypothesis

Patients with AM may have abnormal gut motility. It is postulated that functional abdominal pain results from distension of the GI tract and abnormal contractions which cause hyperalgesia.

A study conducted in a tertiary referral center in Sri Lanka from 2007 to 2012 looked at gastric motility parameters in 17 children aged 4–12 years with AM compared to healthy controls.[30] They found that gastric emptying rate and antral motility parameters were significantly lower in children with AM. Gastric emptying rate had a significant negative correlation with the average duration of pain episodes. The amplitude of antral contractions negatively correlated with scores obtained for severity of symptoms. These findings suggest a possible role of abnormal gastric motility in the pathogenesis of AM.

Altered gut permeability hypothesis

Gut permeability may be altered in patients with AM. Mucosal permeability is an indirect function of gut health. A study conducted by Bentley et al in 1995 compared the gut mucosal permeability between 11 children with diagnosis of AM and healthy controls.[27] They found that gut mucosal permeability was significantly increased in patients with AM when compared to healthy controls. Three patients were followed longitudinally over 3 years with follow-up tests three times a year. They noticed that the gut mucosal permeability decreased with symptomatic improvement and vice versa. This might explain why nonsteroidal anti-inflammatory drugs (NSAIDs) are not beneficial in patients with AM; as these drugs increase mucosal permeability. However, no further research has been conducted to test this hypothesis and its implications in the management of children with AM. Of note, this study was done before specific guidelines were published for the diagnosis of AM.

Diet-induced allergy and altered mucosal immunity hypothesis

Dietary factors may also contribute to the symptoms of AM.[27,31] The role of diet in patients with cephalic migraine has been extensively studied.[32–34] The incidence of cephalic migraine is significantly higher in patients with atopy and other allergic disorders. Certain dietary allergens might trigger mucosal immune responses and manifest the symptoms of AM in susceptible individuals. This hypothesis is further supported by the response of some patients with AM to an oligoantigenic diet with elimination of potential allergens.[17]

In 1995, Bentley et al compared IgE levels and positive radioallergosorbent (RAST) tests in 14 patients with AM and healthy controls.[27] No significant decrease in IgE levels and positive RAST test rate was noted in patients with AM when

compared to the control group. Also, no dietary allergens could be identified via a skin prick test in these patients. This could be because AM causes selective activation of gut mucosal immune response rather than systemic immunity.

In vitro studies have shown that enterocytes can express MHC class II antigen and secrete specific chemokines to stimulate epithelial lymphocytes and activate an immune response under the influence of dietary antigens; more recently, there has been evidence showing that the mucosal immune system is the master regulator of the gut–brain axis.[35] The adaptive immune system (T-cells in particular) and the innate immune system (mucosal lymphoid cells, mast cells, and mononuclear phagocytic cells) play a key role in maintaining gut–brain homeostasis and are disrupted in patients with FGIDs. A disrupted immune system is involved in the pathogenesis of cephalic migraine as well.[36,37]

Further research specifically focused on altered immune responses in patients with AM would help in identifying new treatment strategies.

Abnormal neuroregulation hypothesis

Abnormalities in the metabolism of neurotramitters causing an imbalance between excitatory amino acids and inhibitory amino acids have been well studied in cephalic migraine.[38] A similar mechanism might be involved in the pathogenesis of AM.[39] In the CNS, glutamic acid and aspartic acid are the main excitatory neurotransmitters, whereas gamma aminobutyric acid (GABA) is the inhibitory neurotransmitter. The balance between these two systems regulates the function of other circuits of the brain involving dopamine, serotonin, and norepinephrine. CNS hyperexcitability plays a central role in the pathogenesis of cephalic migraine. Several factors (genetic, environmental, dietary, psychosocial stressors) activate the trigeminovascular system and cause the release of inflammatory neuropeptides and neurotrasmitters including catecholamine gene-related peptide, substance-P, serotonin, adenosine diphosphate, platelet activating factor, nitric oxide resulting in migraine headache. A similar mechanism involving increased activity of excitatory amino acids might play a role in the pathogenesis of AM. This can explain the possible efficacy of certain medications that increase GABA (valproate) in patients with AM.[40]

Phenol sulfotransferase (PST) enzymes (S and P) are key enzymes involved in the metabolism of catecholamines and other amine neurotransmitters. Activity of the enzyme is significantly decreased in patients with diet-induced migraine.[41,42] This results in an accumulation of inflammatory neuropeptides and neurotransmitters that activate the migraine cascade. The enzyme is also inhibited by several dietary constituents including cheese, red wine etc which can all precipitate migraine headache. In 1995, Bentley et al reviewed the platelet expression of these two isoenzymes (PST S and P) in 21 patients with AM when compared to normal subjects.[27] No significant change in enzyme activity was noted in the two groups. The level of enzyme activity in platelets might not be a true reflection of levels in the enteric nervous system. However, more studies are needed to confirm this hypothesis.

Genetic and psychosocial factors

Genetic mutations and polymorphisms of genes, which are still not well defined, regulate ion channels, neurotransmitter metabolism, and mitochondrial metabolism in the CNS and contribute to the pathophysiology of migraine headaches.[43,44] There is a strong genetic predisposition to the development of functional abdominal pain as well.[2] A 2017 study found evidence suggesting Y2 receptor antagonism and YY gene deletion may be related to visceral hyperalgesia.[45] The contribution of genetic factors to AM is further supported by the presence of family history of migraine or chronic abdominal pain in most of the patients.[25,46] However, more research is needed to identify these factors.

Menstrual cycle, pregnancy, lifestyle, diet, anxiety, chronic stress etc are the major psychosocial factors contributing to cephalic migraine.[38] Stress and anxiety also play a role in the pathogenesis of FGIDs.[2] The role of these factors in AM needs to be reviewed in further studies.

Other postulated theories

Autonomic instability, disturbances in the hypothalamus–pituitary axis, altered intestinal microbiome, small intestinal bacterial overgrowth, acute infectious diseases with chronic changes, lactose intolerance, and abnormal mitochondrial function are the other theories that have been proposed in the pathogenesis of FGIDs and cephalic migraine.[2,5] More research focused on pathophysiology of AM needs to be performed to validate the role played by these different factors.

Diagnosis

Clinical features and diagnostic criteria

AM is a well-recognized entity with specific diagnostic criteria under ICHD III (beta version) released in 2013 and Rome IV diagnostic criteria published in 2016.[4] It is included under "episodic syndromes that may be associated with migraine" under the ICHD classification.[5–7] The ICHD defines AM as an idiopathic cause of moderate to severe chronic, recurrent

abdominal pain that is midline, periumbilical, or poorly localized, dull or just sore in quality. Attacks usually last 2–72 hours when not treated successfully or without treatment. Patient is completely free of symptoms between attacks. Patient has at least two associated symptoms among anorexia, nausea, vomiting, and pallor during the attack. At least five "pain episodes" are needed to fulfill the diagnosis.

AM is also included under the Rome classification of FGID and Rome IV criteria recently published in May 2016.[19] As per Rome IV, AM is characterized by paroxysmal episodes of intense periumbilical, midline, or diffuse abdominal pain lasting ≥1 hour. Abdominal pain is the most severe and distressing symptom and is incapacitating and interferes with normal activities. After appropriate evaluation, symptoms cannot be fully explained by another medical condition. The pain may be associated with at least two of the following features: anorexia, nausea, vomiting, headache, photophobia, or pallor. Stereotypical pattern and symptoms are seen in the individual patient. At least two episodes in a 6-month period are needed to confirm the diagnosis.

The two criteria differ in several aspects including the number of episodes required to make the diagnosis and also the duration of each painful episode. As per ICHD III criteria, the patient has to be completely symptom free between the episodes. Rome IV uses the phrase "episodes are separated by weeks to months" to account for baseline GI symptoms and avoid confusion in parents (this replaces the phrase "return to baseline health" in Rome III criteria). Rome IV criteria also remove the dictum that FGID can only be diagnosed after organic diseases are excluded. The usage of "no evidence of organic disease" in Rome III has been replaced with "after appropriate evaluation, symptoms cannot be fully explained by another medical condition." This change allows the clinician to make the diagnosis of AM with selective or no testing. Having a diagnosis of AM does not exclude the presence of other FAPDs for symptoms outside of the episodes.

The average duration of episodes is 1–17 hours and the average number of episodes per month varies from 2 to 20.[17,30,46] Some patients may have more than one episode per day. Headache is the most common associated symptom.

Differential diagnosis

The differential diagnosis for AM includes a list of eclectic conditions that are summarized in Table 1. The paroxysmal nature of the illness, presence of possible triggers, and relieving factors should point to the correct diagnosis before taking recourse to invasive and expensive investigations.[47] The presence of potential alarming signs and symptoms (outlined in Table 2) should caution the clinician to look for other possible organic causes.[2]

Table 1 Abdominal migraine – differential diagnosis

Gastrointestinal disorders
Acid peptic disease (esophagitis, gastritis, peptic ulcer disease)
Eosinophilic diseases (esophagitis, gastritis, enteropathy)
Celiac disease
Gall bladder disease (choledochal cyst, cholelithiasis, cholecystitis)
Gastroesophageal reflex
Small bowel obstruction
Inflammatory bowel disease
Pancreatitis
Other functional abdominal pain disorders (functional dyspepsia, irritable bowel syndrome, cyclic vomiting syndrome, functional abdominal pain – not otherwise specified)
Lactose intolerance
Chronic hepatitis
Surgical causes (hernia, appendicitis, intussusception)
Central nervous system disorders
Posterior fossa disorders
Epilepsy
Intracranial hypertension
Metabolic
Acute intermittent porphyria
Lead poisoning
Diabetes mellitus
Urogenital causes
Urinary tract infection
Ureteropelvic junction obstruction
Nephrolithiasis
Hematologic/oncologic
Sickle cell disease
Tumors (intestinal polyps)
Infectious
Parasitic
Helicobacter pylori gastritis
Pneumonia
Rheumatic
Collagen vascular disease
Others
Foreign body
Munchausen syndrome by proxy
Trauma

Clinical associations

Association with migraine

AM shares many clinical, epidemiologic, and pathophysiologic similarities with cephalic migraine.[25,46] The International Headache Society included AM in the ICHD classification in 2002. A history of migraine headache in a first-degree relative is described in 34%–90% of patients. A personal history of migraine headaches is seen in 24%–47% of patients. AM and cephalic migraine also share common triggers and also similar relieving factors as outlined in

Table 2 Alarm symptoms and signs in children with abdominal migraine

Alarm symptoms
Persistent right upper or right lower quadrant pain
Pain radiating to back
Persistent or bilious vomiting
Gastrointestinal blood loss
Hematuria
Chronic and unexplained diarrhea
Involuntary weight loss
Recurrent or unexplained fever
Dysphagia
Hematochezia, melena
Occult gastrointestinal blood loss
Nocturnal symptoms
Unexplained fever
Family history of inflammatory bowel disease, celiac disease, or familial
Mediterranean fever
Dysuria
Delayed puberty
Joint pain or joint swelling
Alarm signs
Deceleration of linear growth
Signs of peritonitis (rebound, guarding)
Leucocytosis
Hypoalbuminemia
Localized abdominal tenderness, away from umbilicus
Elevated inflammatory markers
Uveitis
Oral lesions
Icterus
Pallor
Rash with no identifiable cause
Organomegaly including hepatomegaly or splenomegaly
Arthritis
Costovertebral angle tenderness
Tenderness over the spine
Perianal abnormalities – anal skin tags, fissures

Table 3 Abdominal migraine: triggers

Bright or flickering light
Poor sleep
Travel
Prolonged fasting
School or family stressors
Dietary triggers (citrus food, caffeine, cheese, chocolate, carbonated drinks, colorings and flavorings)

Table 3. AM has been clearly shown to be a precursor to the development of migraine with and without aura. Also, many of the treatment strategies for migraine have been found to be effective in patients with AM.

A 1995 study by Abu-Arafeh and Russell reviewed the prevalence and clinical features of children with migraine and AM.[46] One hundred and fifty nine children with migraine and 58 children with AM were included in the study. They concluded that patients with migraine and AM shared many similarities to suggest a common pathogenesis. The prevalence of migraine in children with AM was 24%, which was twice the prevalence of migraine in the general population (10%). Conversely, among children with migraine the prevalence of AM was 9%, which was again twice the prevalence of AM in the general population (4.1%). Also, a family history of migraine in a first-degree relative was twice as common in patients with AM when compared to controls (34% vs 17%). Also, patients in the two groups had similar relieving and triggering factors and similar recurrent-associated symptoms.

A study by Good showed that cyclic vomiting syndrome (CVS), AM, and migraine with and without aura share many neurophysiologic similarities including abnormal vision-evoked electroencephalography (EEG)-beta activity, high-frequency photics following responses, and visual event-related potentials.[39] This further supports the classification of AM as a true migraine equivalent.

Of note, migraine is associated with other GI disorders that can be misdiagnosed as AM. Prevalence of migraine is significantly high in patients with celiac disease.[48] Children with migraine can present with abdominal pain and irritable bowel syndrome (IBS)-like symptoms.[48]

Association with other pediatric migraine equivalents

Pediatric migraine variants are a group of paroxysmal, periodic syndromes occurring in patients who have migraine with or without aura, or have an increased propensity to develop migraine. It was previously called childhood periodic syndromes, recurrent pain syndromes, migraine equivalents, or migraine precursors.[49–52]

AM, CVS, benign paroxysmal vertigo, and benign paroxysmal torticollis are episodic syndromes that are associated with migraine headaches.[51,52] AM and CVS were initially thought to be a single disorder and the names were used interchangeably.[53] It was later recognized that they are two separate entities.[54,55] As mentioned earlier, AM and CVS have common electrophysiological characteristics.[39]

Although no association has been shown between AM and benign paroxysmal vertigo, some link has been noted between motion sickness and AM. Farqahar et al reviewed the characteristics of a set of children with symptoms suggestive of AM. He observed that motion sickness was a common complaint in these patients and their families although it was not formally analyzed.[56] A link with motion sickness was further noted in epidemiologic studies conducted in 1983 and 1993.[25,55] Of note, these studies were done when

there were no clear guidelines to diagnose AM. Also, there was no specific demarcation between CVS and AM at that time. Hence, the validity of these observations needs to be further elucidated.

Association with other FAPDs

AM belongs to the class of FAPDs under Rome IV classification of FGIDs. The other disorders included are functional dyspepsia, IBS, CVS, and functional abdominal pain – not otherwise specified. Many of the mechanisms postulated under pathogenesis of AM, especially the visceral hyperalgesia theory, have been studied mostly in patients with FGIDs (IBS and functional dyspepsia, in particular).[57] Helgeland et al noted that symptoms of IBS and AM overlapped in 33% patients as per the Rome III criteria.[19] Clinical association between AM and other FGIDs needs to be evaluated further in research studies as it may open new avenues in the treatment of AM.

Association with atopy and food sensitivity

Studies have shown a correlation between AM and atopy. Patients with cephalic migraine have a higher incidence of atopy and other allergic disorders.[32,33] In addition, dietary modification is central in the management of AM in a similar way as in cephalic migraine.[34]

Bentley et al in 1995 studied the response of 12 patients with symptoms suggestive of AM to a modified dietary regimen avoiding potential allergens. Ten out of the 12 patients (83%) became symptom free or had diminished symptoms with dietary changes. Five out of 12 patients (41%) had a history of eczema, hay fever, or other forms of atopy.[27]

Prognosis

AM is considered as a precursor to cephalic migraine although abdominal pain is proven to resolve completely in most of the patients. Dignan et al studied 54 patients with diagnosis of AM and followed them up for 10 years.[17] Abdominal pain symptoms had resolved completely in 61% cases. In all, 70% developed migraine with or without aura compared with 20% of the matched control group. AM can also rarely persist in adulthood.[58] Longitudinal studies are needed to study long-term prognosis and the course of childhood AM into adulthood.

Evaluation

AM is a subjective diagnosis based on specific symptom-based guidelines as outlined by ICHD III and Rome IV. There are no proven objective markers to correctly make the diagnosis.[59,60] Abnormal EEG changes with visual stimulation have been noted in patients with AM.[39] However, these changes are nonspecific and need further validation. A complete history and physical examination are of utmost importance. A thorough dietary and social history check should be obtained and the growth charts should also be evaluated. Patients should be carefully evaluated for the presence of any potential alarming symptoms or signs (Table 2). Further testing and imaging studies (as outlined in Table 4) should be reserved specifically for patients in whom there are alarm symptoms or if there is a high suspicion of an organic disease.[2] It is a common misconception that further testing reduces anxiety. On the other hand, negative test results reinforce the fear of an unknown organic disease and worsen anxiety in both the patient and family.[2]

Scicchitano et al proposed an algorithm in 2014 to achieve a timely diagnosis of AM which we modified based on the updated Rome IV guidelines (Figure 1).[61] If the diagnosis is still unclear or if there is any suspicion of an organic pathology, the patient should be referred to a pediatric gastroenterologist. To summarize, a comprehensive history and physical examination with judicious use of diagnostic tools would be optimal in making a diagnosis of AM.

Table 4 Diagnostic studies that should be considered in children presenting with chronic and recurrent abdominal pain

Blood studies
Full blood count
Erythrocyte sedimentation rate
C-reactive protein
Electrolytes
Urea and creatinine
Glucose
Liver function tests
Amylase and lipase
Celiac antibodies
Pregnancy test
Urine and stool studies
Urinalysis with microscopy, culture, and sensitivity
Stool occult blood and microscopy
Stool test for *Helicobacter pylori* antigen
Fecal calprotectin
Radiological studies
Abdominal X-ray
Ultrasound of the abdomen and pelvis
Contrast study of upper gastrointestinal tract and small bowel
Magnetic resonance imaging of brain
Endoscopic procedures
Esophagogastroduodenoscopy
Colonoscopy

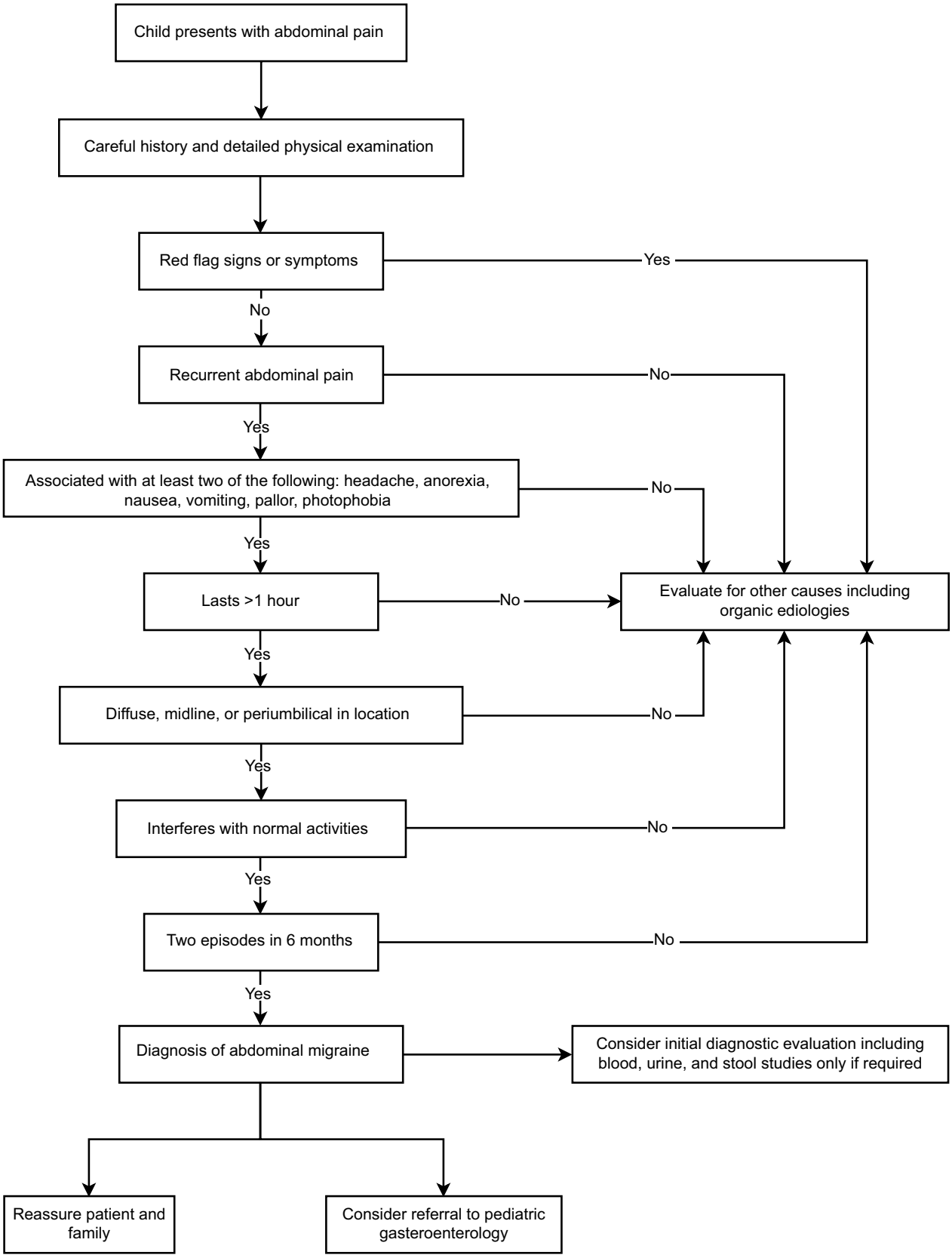

Figure 1 Diagnostic algorithm for abdominal migraine.

Management strategies

There are no definitive guidelines for the management of AM due to extreme paucity of studies in the literature.[60,62] Most of the treatment options are based on few studies in relatively small numbers of children, anecdotal evidence, and close association of AM with migraine headaches and FGIDs.[62] The present treatment options are summarized in Table 5. Nonpharmacotherapeutic interventions including explanation and reassurance, avoidance of triggers, and dietary modifications should be the initial step in management. Drug therapy should be considered only when these primary interventions fail.[15,61]

Non pharmacotherapy

Explanation and reassurance

Explanation and reassurance in a biopsychosocial model of care should be the initial step once a clinical diagnosis of AM is made.[15,61] The parent/child dyad should be educated about the episodic nature of the illness, presence of possible triggers and relieving factors, association with migraine and other FGIDs, and prognosis of the disease based on available data. The absence of any organic abdominal pathology should be reiterated. In addition, a positive outlook that AM is eventually expected to improve on its own in most children will help cope with symptoms.

Avoidance of triggers

AM and migraine share many common triggers as shown in previous studies.[46] Many patients report improvement by avoiding triggers such as stress, travel, exercise, flickering lights, prolonged fasting, and alteration of sleep pattern. Russell et al observed that AM that starts early in the morning can be prevented by taking a breakfast cereal before going to bed.[15] This "breakfast at bedtime" should consist of a high-fiber cereal to prolong its glycemic effect. Further studies are needed to confirm its efficacy.

Table 5 Treatment of abdominal migraine

Nonpharmacologic therapy
Explanation and reassurance
Avoidance of triggers
Modified diet
Psychotherapy
Pharmacotherapy
Abortive therapy
Intranasal sumatriptan
IV valproate
Prophylactic therapies
Beta blocker: propranolol
5-HT antagonists: cyproheptadine
Calcium channel blockers: flunarizine
5-HT agonist with antihistamine properties: pizotifen

Abbreviations: IV, intravenous; HT, hydroxytryptamine.

Dietary management

Dietary modifications recommended in migraine may also be effective in patients with AM. Avoidance of dietary triggers (mentioned in Table 3) may be helpful in some patients. A diet low in amines may also aid in reducing the frequency and severity of attacks. An oligoantigenic diet or few foods diet may be helpful in patients having frequent bouts of abdominal pain.[34] This is implemented by restricting the diet initially and gradually reintroducing foods in an attempt to identify specific foods that may be affecting the individual patient. Russell et al reported a favorable outcome in 17 out of 22 patients (77%) treated with an oligoantigenic diet.[15]

A high-fiber diet may also be effective in some patients with recurrent abdominal pain.[63] Probiotics have been found to be effective in patients with FAPDs, especially IBS and functional dyspepsia.[63] Lactose intolerance has been noted in some patients with chronic abdominal pain and a lactose-free diet is effective in this subgroup.[2,63] However, further research needs to be carried out to study the efficacy of these treatment options in children with AM.

Behavior therapy

Psychotherapy, specifically cognitive behavior therapy, may be effective in patients with AM. The biopsychosocial model of origin of functional abdominal pain suggests that psychological interventions may be helpful in these patients. Hypnotherapy, family therapy, and yoga have been found to be beneficial in children with functional abdominal pain, IBS in particular.[64,65] More studies focused specifically on AM need to be carried out to prove the efficacy of these treatment options.

Pharmacotherapy

Pharmacotherapy is reserved for patients with frequent, severe symptoms or for those patients who do not respond well to nonpharmacological interventions.[15] As there is no objective measurement of disease severity, the decision to start drug therapy is based on the clinician's judgment and receptiveness of the family to various treatment options. Studies related to the use of these drugs in AM are summarized in Table 6.

Table 6 Abortive and prophylactic therapy in abdominal migraine

Study	Mechanism of action	Type of study	Participants	Interventions	Results
Abortive therapy with sumatriptan (Kakisaka et al)[66]	Serotonin/5-hydroxytryptophan agonist (5-HT ID)	Case report (2010)	1 child with abdominal migraine	Intranasal sumatriptan for acute attack of abdominal pain	Complete resolution of pain
Abortive therapy with IV valproate (Tan et al)[40]	GABA agonist	Case report (2006)	2 children with abdominal migraine	IV valproate	Symptomatic relief
Prophylactic therapy with cyproheptadine (Madani et al)[70]	First-generation antihistamine with anti-serotoninergic and calcium channel blocking properties	Retrospective study (2016)	18 children with abdominal migraine	0.13–0.2 mg/kg/day	72% of patients with improvement in symptoms
Prophylactic therapy with flunarizine (Kothare)[68]	Calcium channel blocker	Clinical trial (2005)	8 children with abdominal migraine	7.5 mg daily PO	61% reduction in frequency and 51% reduction in duration
Prophylactic therapy with propranolol vs cyproheptadine (Worawattanakul et al)[62]	Propranolol – beta blocker Cyproheptadine – first-generation antihistamine with anti-serotoninergic and calcium channel blocking properties	Retrospective study (1999)	36 children with abdominal migraine (12 treated with cyproheptadine; 24 treated with propranolol)	Cyproheptadine 0.25–0.5 mg/kg/day of propranolol 10–20 mg BID–TID	33% complete resolution, 50% fair response, 17% no response 75% excellent response, 8% fair response, 17% no response
Prophylactic therapy with pizotifen syrup (Symon and Russell)[69]	Serotonin antagonist (5-HT 2A and 2D)	Double-blind placebo controlled trial (1995)	14 children with abdominal migraine	5 mL BID to TID (0.25 mg/5 mL)	Effective in 70% of patients

Abbreviations: HT, hydroxytryptamine; BID, twice a day; TID, thrice a day; PO, orally; GABA, gamma aminobutyric acid; IV, intravenous.

Abortive therapy

Triptans (5-hydroxytryptophan 1 A/D agonists) have been found to be effective for abortive therapy. Intranasal sumatriptan therapy has been studied in patients with AM.[66] Almotriptan has been found to be effective in patients with pediatric migraine.[67] However, no studies have been conducted on patients with AM. The efficacy of NSAIDs and acetaminophen needs to be studied with well-designed randomized control trials.

Prophylactic therapy

Beta blockers (propranolol), calcium channel blockers (flunarizine), serotonin antagonists (cyproheptadine, pizotifen), and GABA agonists (valproate) are the most common drugs that have used in patients with AM.[40,62,68–70] These drugs have been found to be effective in patients with cephalic migraine and hence were tried in patients with AM due to similarities in their pathogenesis.

Scicchitano et al recommend propranolol as the first-line choice of drug therapy when non-pharmaceutical interventions fail. Cyproheptadine is recommended as the second-line agent when propranolol is ineffective or contraindicated.[61]

Conclusion

AM is a FAPD characterized by paroxysmal episodes of periumbilical pain and other vasomotor or GI symptoms severe enough to interfere with daily activities. It is considered as a precursor of migraine headaches and shares a similar pathophysiology and treatment responses. A comprehensive history, physical examination, appropriate diagnostic tests (only if needed), and use of well-defined guidelines will aid in the timely diagnosis of AM and optimize treatment outcomes.

Although precise diagnostic criteria are present, it continues to be an underdiagnosed entity. Increasing awareness among the scientific community combined with more research studies focusing on epidemiology, pathophysiology, effective treatment options, and long-term prognosis would help improve the quality of life of affected children and limit health care utilization.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Di Lorenzo C, Colletti RB, Lehmann HP, et al. Chronic abdominal pain in children: a technical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition: AAP Subcommittee and NASPGHAN Committee on Chronic Abdominal Pain. *J Pediatr Gastroenterol Nutr.* 2005;40(3):249–261.
2. McFerron BA, Waseem S. Chronic recurrent abdominal pain. *Pediatr Rev.* 2012;33(11):509–517.
3. Feldman W, Rosser W, McGrath P. Recurrent abdominal pain in children. *Can Fam Physician*. 1988;34:629–630.
4. Drossman DA, Hasler WL. Rome IV – functional GI disorders: disorders of gut-brain interaction. *Gastroenterology*. 2016;150(6):1257–1261.
5. Napthali K, Koloski N, Talley NJ. Abdominal migraine. *Cephalalgia.* 2016;36(10):980–986.
6. Winner P. Abdominal migraine. *Semin Pediatr Neuro.* 2016;23(1): 111–113.
7. Wang SJ. Abdominal migraine. In:Greenamyre JT, editor. *MedLink Neurology* [Online October 8, 2016]. San Diego, CA: MedLink Corp; 2013.
8. Carson L, Lewis D, Tsou M, et al. Abdominal migraine: an underdiagnosed cause of recurrent abdominal pain in children. *Headache.* 2011;51(5):707–712.
9. Blitzstein NL, Brams WA. Migraine with abdominal equivalent. *J Am Med Assoc.* 1926;86(10):675–677.
10. Wyllie WG, Schlesinger B. The periodic group of disorders in childhood. *Br J Child Dis.* 1933;30:1–21.
11. Symon DN, Russell G. Abdominal migraine: a childhood syndrome defined. *Cephalalgia.* 1986;6(4):223–228.
12. Axon AT, Long DE, Jones SC. Abdominal migraine: does it exist*? J Clin Gastroenterol.* 1991;13(6):615–616.
13. Symon DN, Hockaday JM. Is there a place for "abdominal migraine" as a separate entity in the IHS classification? Yes! *Cephalalgia.* 1992;12(6):345–348.
14. Hockaday JM. Is there a place for" abdominal migraine" as a separate entity in the IHS classification? No! *Cephalalgia*.1992;12(6):346.
15. Russell G, Abu-Arafeh I, Symon DN. Abdominal migraine: evidence for existence and treatment options. *Paediatr Drugs*. 2002;4(1):1–8.
16. Russell G, Symon DN, Abu-Arafeh IA. The child with recurrent abdominal pain: is it abdominal migraine? *Br J Hosp Med*. 2007;68(7):M110–M113.
17. Dignan F, Abu-Arafeh I, Russell G. The prognosis of childhood abdominal migraine. *Arch Dis Child.* 2001;84(5):415–418.
18. Uc A, Hyman PE, Walker LS. Functional gastrointestinal disorders in African American children in primary care. *J Pediatr Gastroenterol Nutr* 2006;42(3):270.
19. Helgeland H, Flagstad G, Grøtta J, Vandvik PO, Kristensen H, Markestad T. Diagnosing pediatric functional abdominal pain in children (4–15 years old) according to the Rome III Criteria: results from a Norwegian prospective study. *J Pediatr Gastroenterol Nutr.* 2009;49(3):309–315.
20. Devanarayana NM, Adhikari C, Pannala W, Rajindrajith S. Prevalence of functional gastrointestinal diseases in a cohort of Sri Lankan adolescents: comparison between Rome II and Rome III criteria. *J Trop Pediatr.* 2011;57(1):34–39.
21. Korterink JJ, Diederen K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. *PLoS One*. 2015;10(5):e0126982.
22. Lewis ML, Palsson OS, Whitehead WE, Van Tilburg MA. Prevalence of functional gastrointestinal disorders in children and adolescents. *J Pediatr.* 2016;177:39–43.
23. Játiva E, Velasco-Benítez CA, Koppen IJ, Játiva-Cabezas Z, Saps M. Prevalence of functional gastrointestinal disorders in schoolchildren in Ecuador. *J Pediatr Gastroenterol Nutr*. 2016;63(1):25–28.
24. Devanarayana NM, Mettananda S, Liyanarachchi C, et al. Abdominal pain–predominant functional gastrointestinal diseases in children and adolescents: prevalence, symptomatology, and association with emotional stress. *J Pediatr Gastroenterol Nutr.* 2011;53(6):659–665.
25. Mortimer MJ, Kay J, Jaron A. Clinical epidemiology of childhood abdominal migraine in an urban general practice. *Dev Med Child Neurol.* 1993;35(3):243–248.
26. Chitkara DK, Rawat DJ, Talley NJ. The epidemiology of childhood recurrent abdominal pain in Western countries: a systematic review. *Am J Gastroenterol.* 2005;100(8):1868–1875.
27. Bentley D, Kehely A, Al-Bayaty M, Michie CA. Abdominal migraine as a cause of vomiting in children. *J Pediatr Gastroenterol Nutr.* 1995;21:S49–S51.
28. Baber KF, Anderson J, Puzanovova M, Walker LS. Rome II versus Rome III classification of functional gastrointestinal disorders in pediatric chronic abdominal pain. *J Pediatr Gastroenterol Nutr.* 2008;47(3):299.
29. Korterink J, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA. Childhood functional abdominal pain: mechanisms and management. *Nat Rev Gastroenterol Hepatol.* 2015;12(3):159–171.
30. Devanarayana NM, Rajindrajith S, Benninga MA. Abdominal migraine in children: association between gastric motility parameters and clinical characteristics. *BMC Gastroenterol.* 2016;16(1):26.
31. Bentley D, Katachburian A, Brostoff J. Abdominal migraine and food sensitivity in children. *Clin Allergy.* 1984;14(5):499–500.
32. Mehle ME. Migraine and allergy: a review and clinical update. *Curr Allergy Asthma Rep*. 2012;12(3):240–245.
33. Özge A, Öksüz N, Ayta S, et al. Atopic disorders are more common in childhood migraine and correlated headache phenotype. *Pediatr Int.* 2014;56(6):868–872.
34. Egger J, Wilson J, Carter CM, Turner MW, Soothill JF. Is migraine food allergy? A double-blind controlled trial of oligoantigenic diet treatment. *Lancet.* 1983;322(8355):865–869.
35. Powell N, Walker MM, Talley NJ. The mucosal immune system: master regulator of bidirectional gut-brain communications. *Nat Rev Gastroenterol Hepatol.* 2017;14(3):143–159.
36. Goadsby PJ. Pathophysiology of migraine. *Ann Indian Acad Neurol.* 2012;15(Suppl 1):S15–S22.
37. Loewendorf AI, Matynia A, Saribekyan H, Gross N, Csete M, Harrington M. Roads less traveled: sexual dimorphism and mast cell contributions to migraine pathology. *Front Immunol.* 2016;7:140.
38. D'Andrea G. Pathogenesis of chronic migraine: the role of neuromodulators. *J Headache Pain*. 2015;16(S1):A38.
39. Good PA. Neurologic investigations of childhood abdominal migraine: a combined electrophysiologic approach to diagnosis. *J Pediatr Gastroenterol Nutr.* 1995;21(Suppl 1):S44–S48.
40. Tan V, Sahami AR, Peebles R, Shaw RJ. Abdominal migraine and treatment with intravenous valproic acid. *Psychosomatics*. 2006;47(4):353–355.
41. Jones AL, Rubin GL, Coughtrie MW, Roberts RC, Colvin W. Reduced platelet phenolsulphotransferase activity towards dopamine and 5-hydroxytryptamine in migraine. *Eur J Clin Pharmacol.* 1995;49(1):109–114.
42. Gibb C, Glover V, Gilbertson N, Bentley D, Sandler M. Platelet phenolsulphotransferase activity and 'abdominal migraine'. *Arch Dis Child.* 1988;63(12):1500–1501.
43. Kusumi M, Ishizaki K, Kowa H, et al. Glutathione S-transferase polymorphisms: susceptibility to migraine without aura. *Eur Neurol.* 2003;49(4):218–222.
44. Mortimer MJ, Kay J, Jaron A, Good PA. Does a history of maternal migraine or depression predispose children to headache and stomach ache? *Headache.* 1992;32(7):353–355.
45. Hassan AM, Jain P, Mayerhofer R, et al. Visceral hyperalgesia caused by peptide YY deletion and Y2 receptor antagonism. *Sci Rep.* 2017;7: 40968.
46. Abu-Arafeh I, Russell G. Prevalence and clinical features of abdominal migraine compared with those of migraine headache. *Arch Dis Child.* 1995;72(5):413–417.

47. Sangermani R, Pirovano S, Vaccari R, Gibelli M, Rossi A. Abdominal migraine simulating acute abdomen. *Pediatr Med Chir.* 1991;14(2):163–165.
48. Dimitrova AK, Ungaro RC, Lebwohl B, et al. Prevalence of migraine in patients with celiac disease and inflammatory bowel disease. *Headache.* 2013;53(2):344–355.
49. Cuvellier JC, Lépine A. Childhood periodic syndromes. *Pediatr Neurol.* 2010;42(1):1–11.
50. Lanzi G, Balottin U, Fazzi E, Rosano FB. The periodic syndrome in pediatric migraine sufferers. *Cephalalgia.* 1983;3(1_Suppl):91–93.
51. Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Childhood periodic syndromes: a population-based study. *Pediatr Neurol.* 2010;43(6):420–424.
52. Lagman-Bartolome AM, Lay C. Pediatric migraine variants: a review of epidemiology, diagnosis, treatment, and outcome. *Curr Neurol Neurosci Rep.* 2015;15(6):1–4.
53. Symon DN. Is cyclical vomiting an abdominal form of migraine in children? *Dig Dis Sci.* 1999;44(8 Suppl):23S–25S.
54. Catto-Smith AG, Ranuh R. Abdominal migraine and cyclical vomiting. *Semin Pediatr Surg.* 2003;12:254–258.
55. Lanzi G, Balottin U, Ottolini A, Burgio FR, Fazzi E, Arisi D. Cyclic vomiting and recurrent abdominal pains as migraine or epileptic equivalents. *Cephalalgia.* 1983;2:115–118.
56. Farquhar HG. Abdominal migraine in children. *Br Med J*. 1956;1(4975); 1082–1085.
57. Bremner AR, Sandhu BK. Recurrent abdominal pain in childhood: the functional element. *Indian Pediatr.* 2009;46(5):375–379.
58. Kunishi Y, Iwata Y, Ota M, Kurakami Y, Matsubayashi M, Kanno M. Abdominal migraine in a middle-aged woman. *Intern Med*. 2016;55(19):2793.
59. Popovich DM, Schentrup DM, McAlhany AL. Recognizing and diagnosing abdominal migraines. *J Pediatr Health Care*. 2010;24(6):372–377.
60. Lundberg PO. Abdominal migraine-diagnosis and therapy. *Headache.* 1975;15(2):122–125.
61. Scicchitano B, Humphreys G, Mitton SG, Jaiganesh T. Abdominal migraine in childhood: a review. *Pediatr Health Med Ther.* 2014;5:73–81.
62. Worawattanakul M, Rhoads JM, Lichtman SN, Ulshen MH. Abdominal migraine: prophylactic treatment and follow-up. *J Pediatr Gastroenterol Nutr.* 1999;28(1):37–40.
63. Newlove-Delgado TV, Martin AE, Abbott RA, et al. Dietary interventions for recurrent abdominal pain in childhood. *Cochrane Database Syst Rev*. 2017;3:CD010972.
64. Palsson OS. Hypnosis treatment of gastrointestinal disorders: a comprehensive review of the empirical evidence. *Am J Clin Hypn.* 2015;58(2):134–158.
65. Gulewitsch MD, Weimer K, Enck P, Schwille-Kiuntke J, Hautzinger M, Schlarb AA. Stress reactivity in childhood functional abdominal pain or irritable bowel syndrome. *Eur J Pain.* 2017;21(1):166–177.
66. Kakisaka Y, Wakusawa K, Haginoya K, et al. Efficacy of sumatriptan in two pediatric cases with abdominal pain-related functional gastrointestinal disorders: does the mechanism overlap that of migraine? *J Child Neurol.* 2010;25(2):234–237.
67. Kacperski J, Hershey AD. Newly approved agents for the treatment and prevention of pediatric migraine. *CNS Drugs.* 2016;30(9):837–844.
68. Kothare SV. Efficacy of flunarizine in the prophylaxis of cyclical vomiting syndrome and abdominal migraine. *Eur J Paediatr Neurol*. 2005;9(1):23–26.
69. Symon DN, Russell G. Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. *Arch Dis Child.* 1995;72(1):48–50.
70. Madani S, Cortes O, Thomas R. Cyproheptadine use in children with functional gastrointestinal disorders. *J Pediatr Gastroenterol Nutr.* 2016;62(3):409–413.