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Review

Brain to Belly: Abdominal Variants of Migraine and Functional Abdominal Pain Disorders Associated With Migraine

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Migraine is one of the most frequent causes of primary headache and 9% of children suffer from migraines. Most children will continue to experience migraine attacks as adults, therefore it is imperative that we have a thorough understanding of this major health issue. This article considers the so-called abdominal variants of migraine, which are more commonly seen in children rather than adults: abdominal migraine, cyclic vomiting syndrome, and infantile colic. Other functional abdominal pain disorders such as irritable bowel syndrome and functional dyspepsia have also been linked to migraine in clinical studies. The common pathophysiological root of these diseases seems to be the gut-brain axis mechanism. Abdominal variants of migraine are considered pediatric precursors of migraine whereas the functional abdominal pain disorders related to migraine seem to share a pathophysiological root with no temporarily link as for today. In this review we aim to describe the epidemiological background, the current pathophysiological theories and the relationship of each disease to migraine. This review is the first to compile abdominal variants of migraine and functional abdominal pain disorders associated with migraine and we endeavor to elucidate the broad spectrum of migraine-related episodes in children.

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Key Words
Abdominal pain; Child; Gastrointestinal microbiome; Migraine disorders

Introduction

Migraine is one of the most frequent types of primary headache. In 2015, the Global Burden of Disease Study ranked it third as a cause of disability for men and women under 50 years of age.[1] In 2017, the European prevalence of migraine was 20%, which was a 6% increase compared to 1997.[2]

In the pediatric population, the most recent epidemiological study[3] estimated the prevalence of migraine to be 9.1%, and cross-sectional studies underline a constant increase of incidence of migraine with and without aura.[4] Understanding the epidemiology and the prognosis of migraines in children and adolescents is important since the majority will continue to suffer into adulthood.[3,5]

Pediatric migraines differ from those experienced by adults, thus, their diagnosis can be challenging. Firstly, the diagnostic

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criteria are different:[6] episodes are commonly bilateral (whereas they are typically unilateral for adults) and shorter (sometimes less than one hour, especially for young children).[7] Secondly, we now acknowledge a broad spectrum of migraine-related episodes which are more frequently seen in children: abdominal migraine (AM), cyclic vomiting syndrome (CVS), and infantile colic.[8] These episodes can have a great impact on the child's and parent's quality of life,[9] particularly since migraineur children are frequently afflicted with other comorbidities. Obesity,[10] atopy, or allergic disease,[11] a dysfunctional family situation, a low level of physical activity and physical or emotional abuse have all been associated with migraine and to its onset or progression.[12] The relationship between migraine and functional abdominal pain has been discussed at length among adults[13-15] and identifies a connection between migraine and irritable bowel syndrome (IBS) and functional dyspepsia (FD), but further research is required among the pediatric population.[16]

These studies are evidence for the scholarly interest in understanding the pathophysiology behind migraines. The pathophysiology of migraine is a multifactorial phenomenon,[17] dependent on genetic factors (more than thirty migraine-associated gene polymorphisms have been discovered),[18] environmental factors (such as medication, diet, and stress) and metabolic factors (examples include neuroendocrine function, the menstrual cycle, and pregnancy). The activation of the hypothalamus results in an alteration in thalamocortical circuits and brain connectivity, which subsequently leads to calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP) release. The release of PACAP triggers intra-cerebral vasodilatation, ultimately causing the symptoms of migraine. Today, the role of CGRP in the gut-brain axis bidirectional communication is well recognized: CGRP has an antimicrobial action on gut bacterial strains (for instance, *Escherichia coli, Enterococcus faecalis*, and *Lactobacillus acidophilus*) and dysbiosis can increase the secretion of CGRP.[19] The communication of the gut immune system, mucosa, and microbiota with the brain has been recently explored in great depth within the field of migraine research, particularly the association between functional abdominal pain disorders and migraine.[19,20] The main communication pathways of the gut-brain axis are represented in Figure.

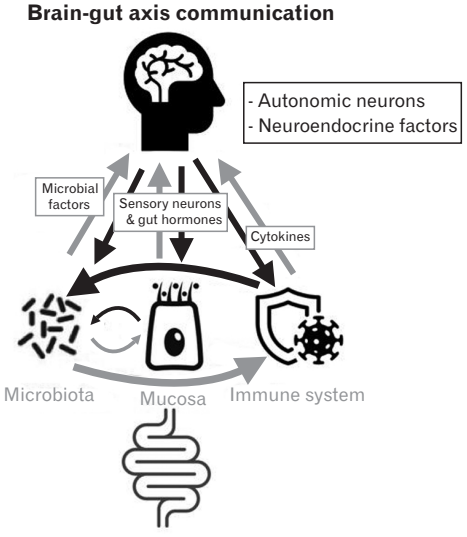

Figure. Gut-brain axis communication. Brain-gut communication describes the bidirectional messages from brain to gut microbiota, mucosa and immune system and vice versa, as well as the communication of the microbiota with the mucosa and the gut immune system. Microbial factors, gut hormones, sensory neurons, and cytokines can modify cerebral function. Autonomic neurons and neuroendocrine factors can modify the gut behavior in return.

The diagnosis of migraine, its abdominal variants and functional abdominal pain can be challenging as they are often associated with each other. Early diagnosis is a good prognostic indicator of recovery for children and adolescents suffering from functional abdominal pain[21] and migraines,[5] thus the recognition of those conditions can have a great impact on children's quality of life.

To date, reviews have studied either the association of abdominal variants or the functional abdominal pain disorders with migraine (Table 1).[13,22-30] In this review, we aim to define the different abdominal variants of migraine (AM, CVS, and infantile colic) and the functional abdominal pain disorders associated with migraine (IBS and dyspepsia) (Table 2), to describe their relation to migraine (Table 3), their epidemiology and their evolution within the pediatric population, and finally to discuss current therapeutic management.

Abdominal Variants of Migraine

AM, CVS, and infantile colic are gastrointestinal episodic syndromes classified as variants of migraine by the international classification of headache disorders (ICHD)-3 (beta version).[8] Among the episodic syndromes, we also acknowledge benign paroxysmal vertigo and benign paroxysmal torticollis, but these 2 conditions will not be discussed here as they do not involve the gastrointestinal tract.

Abdominal Migraine

AM has been described in children since 1984 by Symon and Russel[31] and is now part of both the ICHD classification, and the

Table 1. Previous Reviews on Abdominal Variants of Migraine and Functional Abdominal Pain Disorders' Association to Migraine

Subject of study	Study	Authors	Year of publication
Abdominal variants of migraine	Migraine and childhood periodic syndromes in children and adolescents	Gelfand[22]	2013
	Pediatric migraine and episodic syndromes that may be associated with migraine	Spiri et al[23]	2014
	Migraine equivalents as part of migraine syndrome in childhood	Tarantino et al [24]	2014
	Migraine variants or episodic syndromes that may be associated with migraine and other unusual pediatric headache syndromes	Rothner and Parikh[25]	2016
	Recurrent gastrointestinal disturbance: abdominal migraine and cyclic vomiting syndrome	Irwin et al[26]	2017
Cyclic vomiting syndrome	Cyclic vomiting syndrome and migraine in children	Lin et al[27]	2011
Infantile colic	The relation between migraine and infantile colic: a systematic review and meta-analysis	Gelfand et al[28]	2015
	The link between infantile colic and migraine	Qubty and Gelfand[29]	2016
	Relation between infantile colic and migraine as well as tension-type headache: a meta-analysis	Zhang et al[30]	2019
Functional gastrointestinal disorders	Migraine associated with gastrointestinal disorders: review of the literature and clinical implications	van Hemert et al[13]	2014

Rome IV classification.[32] The diagnosis of AM can be challenging as it is at the crossroads of multiple organ's symptomatology. A positive clinical diagnosis of AM avoids unnecessary treatments and investigations.

A pragmatic clinical definition of AM in children is given by Angus-Leppan et al[33] in 2018, adapted from definitions of Symon and Russel,[31] ICHD-3 beta,[8] and Rome IV[32]: (1) episodic central abdominal pain, usually lasting > 1 hour, (2) episodes interfere with normal activity, (3) episodes occur with one or more of pallor, anorexia, nausea, vomiting, photophobia, headache, or are associated with other episodic syndromes (particularly CVS well between episodes), and (4) normal physical and developmental examination.

Children with AM report similar triggers (stress and fatigue) and relieving factors (rest and sleep) to migraineurs.[34] One key to the diagnosis is the absence of headache during episodes. Vomiting symptoms are also less severe than in CVS. The prevalence of AM is generally reported to be around 5% to 9% of the pediatric population[34,35] but increases in children with a family history of migraine or depression.[34-37] It is also higher among girls, with a reported sex ratio around 1.6/1 in Abu-Arafeh's first prevalence study in 1995.[34]

In the adult population, the diagnosis of AM remains very uncommon and few case reports have been published to date.[38] Roberts and deShazo[39] reported a cohort of 13 patients (11 from the medical literature and 2 from their clinic) and analyzed their symptoms by the IHCD-2 and the Rome III classifications of pediatric AM: 10 of their patients met some criteria for AM. Ninety percent of them had a family history of migraine.[39] Their findings suggest considering AM in the differential diagnosis of recurrent abdominal pain in adults, especially if a family history of migraine is observed.

With respect to the pathophysiology hypothesis, in 2016, Devanarayana et al[40] studied gastric motility of AM patients compared with control patients and showed that gastric and antral motility parameters were significantly lower in children with AM. They also noticed a significant correlation between symptom severity and gastric motility, a field of study within gut-brain axis diseases since it aids our understanding of the central innervation of the gut. Moreover, alteration of gut permeability has been proven in AM patients. In a study of 11 AM patients and 9 control children, Bentley et al[37] showed that the mucosal permiability of small intestine was increased in AM patients. Furthermore, they longitudinally followed 3 AM patients and noticed a decrease in gut permeability correlated to the improvement of the AM symptoms. In some patients, the mucosal response to food allergens evidently seemed to trigger AM.[37] The communication between the enteric and the central nervous system (CNS), best known as the gut-brain axis, helps us to understand how these intestinal changes are related to migraine.[41]

Children with AM have an excellent prognosis, with a majority demonstrating complete resolution of symptoms. It is unclear what causes AM to persist into adulthood since there are few case reports

Table 2. Abdominal Variants of Migraine and Functional Abdominal Pain Disorders Associated to Migraine

Pathology	Clinical definition	Source
Abdominal migraine	Episodic central abdominal pain, usually lasting > 1 hour Episodes interfere with normal activity Episodes occur with one or more of pallor, anorexia, nausea, vomiting, photophobia, and headache, or are associated with other episodic syndromes (particularly cyclic vomiting syndrome and migraine limb pain) The person is well between episodes and has a normal physical and developmental examination	Adapted from ICHD-3b[a] and Rome IV classification
Cyclic vomiting syndrome	Recurrent episodic attacks of intense nausea and vomiting, usually stereotypical in the individual and with predictable timing of episodes Attacks may be associated with pallor and lethargy There is a complete resolution of symptoms between attacks The diagnostic criteria include all of the following: Nausea and vomiting occurring at least 4 times per hour Attacks lasting from 1 hour up to 10 days Attacks occurring 1 week apart	ICHD-3b[a] criteria
Infantile colic	A. Recurrent episodes of irritability, fussing, or crying from birth to 4 months of age, fulfilling criterion B: B. Both of the following: Episodes last for 3 hours per day Episodes occur on 3 days per week for 3 weeks Not attributed to another disorder	ICHD-3b[a] criteria
Irritable bowel syndrome	Abdominal pain at least 4 days per month associated with one or more of the following: Related to defecation A change in frequency of stool A change in form (appearance) of stool In children with constipation, the pain does not resolve with resolution of the constipation (in this case, the child has functional constipation) After appropriate evaluation, the symptoms cannot be fully explained by another medical condition	Rome IV classification
Functional dyspepsia	One or more of the following symptoms at least 4 days per month: Postprandial fullness Early satiation Epigastric pain or burning not associated with defecation After appropriate evaluation the symptoms cannot be fully explained by another medical condition	Rome IV classification

[a]International classification of headache disorders (ICHD)-3 (beta version).

and small sample sizes.[39] Although AM symptoms ultimately tend to evanesce, almost 70% of children will go on to develop classic migraine or recurrent abdominal pain syndrome.[42,43]

AM is now considered to be a pediatric precursor of migraine, consequently experts tend to extrapolate the usual migraine treatment to AM. However, to date, only 1 randomized control trial has been published within the field of pediatrics: pizotifen (a serotonin agonist) reduces the duration and the severity of AM when used as a preventive treatment[44] Retrospective data on propranolol (a β blocker), cyproheptadine (an antihistamine), and flunarizine (a calcium channel blocker) as preventive therapies also seem to show a reduction in the frequency and severity of AM episodes.[33] Lifestyle modifications are also recommended to prevent migraine crises.

Cyclic Vomiting Syndrome

CVS is part of the episodic syndromes associated with migraine as defined by the ICHD-3b classification.[8] The symptoms of CVS are very typical and have been recently defined as[8]: (1) recurrent

Table 3. Pathophysiological, Clinical, and Temporal Relation of Abdominal Migraine, Cyclic Vomiting Syndrome, Infantile Colic, Irritable Bowel Syndrome, and Functional Dyspepsia With Migraine

Pathology	Common physiopathology	Common clinical features	Temporal course
Abdominal migraine	Gastric motility alteration Increased gut permeability	Triggering/relieving factors Family history of migraine	Precursor of migraine in adulthood
Cyclic vomiting syndrome	Neuronal hyperexcitation Gastric motility alteration	Anxiety/depression in personal or family history	Precursor of migraine in adulthood
Infantile colic	Microbiota modification Increased gut inflammation and permeability	Anxiety/depression in personal or family history Family history of migraine	Precursor of migraine in adulthood
Irritable bowel syndrome	Visceral hyperalgesia Increased gut permeability and immune-allergic response	Amelioration of symptoms with FODMAPs exclusive regime Anxiety/depression in personal or family history	Co-occurrence with migraine
Functional dyspepsia	Gastric motility alteration Visceral hyperalgesia Increased immune-allergic response	Anxiety/depression in personal history	Co-occurrence with migraine

FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

episodic attacks of intense nausea and vomiting, usually stereotypical to the individual and with predictable timing of episodes, (2) attacks may be associated with pallor and lethargy, and (3) there is a complete resolution of symptoms between attacks.

The diagnostic criteria include all of the following: (1) nausea and vomiting occurring at least 4 times per hour, (2) attacks lasting from 1 hour up to 10 days, and (3) attacks occurring 1 week apart.

The prodromal phase is characterized by intense nausea, pallor, tiredness, and abdominal pain. The vomiting phase is very intense within the first hour with a median frequency of 6 vomiting episodes per hour, declining during the next 4 hours to 8 hours. The recovery phase begins with the remission of nausea, continuing until recovery of appetite and strength. In 75% of children, the attacks begin between midnight and early morning.[45]

The prevalence of CVS is estimated between 0.3%[46] and 6.1%[47] making it less frequent in the pediatric population than migraine or AM. The pathophysiology of CVS remains unclear but different possibilities have been researched recently. Mitochondrial abnormalities have been explored as a maternal inheritance of CVS and 2 mitochondrial polymorphisms have been found to be highly associated with migrainous headaches and CVS.[48] As with the migrainous pathophysiology, hypothalamic function is also influential in CVS as the control center of the CNS. In 2016, Ellingsen et al[49] published the first functional MRI study to characterize altered brain connectivity in the insular cortex, the region of the brain involved in disease mechanisms responsible for both CVS and adult migraine. Autonomic dysfunction studies show a strong correlation between CVS, postural orthostatic tachycardia and an aberrant heart rate variability.[50] Gastric motility has been explored in pediatric and adult patients suffering from CVS or migraine and mostly shows acceleration of gastric emptying, which implies altered autonomic function.

In comparison to AM, CVS has also been explored in the adult population and it is interesting to compare these cohorts. As children mature, their symptoms generally ameliorate or resolve; attacks become less intense and shorter in duration. In a Taiwanese pediatric study,[51] 9 out of 24 patients were symptom-free 4 years after diagnosis. On the other hand, newly diagnosed adult patients tend to have longer and more intense episodes than children[52] but the vomiting pattern previously described remains consistent.[53] Time to diagnosis is around 2 years for children whereas it is around 8 years for adults. The quality of life of CVS school-age children is often significantly affected; 85% had absences from school in the previous year due to their condition.[45] An early diagnosis improves the quality of life of children suffering from CVS.[54] Considering these data, the psychiatric profile of CVS patients has also been explored,[55] with 1 study finding that 47% of children with CVS suffer from anxiety disorders. It is important to note that in this study parents reported significantly more psychiatric symptoms in their children than the children themselves. The hypothesis of anxiety transmission has also been explored for migraine and infantile colic.

The treatment of CVS in children is the same as for migraine: lifestyle modifications, plus medical management such as propranolol, flunarizine or mirtazapine, or anticonvulsants such as topira-

mate, phenobarbital, or levetiracetam. Antiemetic treatment such as aprepitant can also be used as a preventive treatment in CVS.[56]

Prognostically, it has been demonstrated that between 30% and 50% of CVS patients will develop migraines,[57] with children diagnosed at an early age and those with more severe symptoms being the most likely to become migraineurs. Moreover, the clinical features (nausea, vomiting, and phono-photo-phobia), the periodicity, the triggers (stress and sleep deprivation) allow us to consider CVS as an equivalent and a precursor of migraine in children.

Infantile Colic

Infantile colic has recently been added to the ICHD classification, first appearing in the 2013 ICHD-3b.[8] Infantile colic was first described and characterized by Wessel et al[58] in 1954 to describe the "paroxysmal fussing" of infants under 4 months of age. It describes "paroxysmal fussing" or "infantile colic" as "possibly one of the earliest somatic responses to the presence of tension in the environment" leading to years of understanding infantile colic as a type of psychosomatic disorder. The ICHD classification's diagnosis criteria are as follows: (1) A. Recurrent episodes of irritability, fussing, or crying from birth to 4 months of age, fulfilling criterion B; (2) B. Both of the following: episodes last for 3 hours per day and episodes occur on 3 days per week for 3 weeks; and (3) not attributed to another disorder.

A systematic review and meta-analysis of 2017 by Wolke et al[59] studied the prevalence and crying duration of infantile colic and reported a high prevalence, 17-25%, of infantile colic under 6 weeks, decreasing shortly after 6 weeks to 11% and to 0.6% by 10-12 weeks.

The pathophysiology of infantile colic is also a good model of the gut-brain axis mechanism. The influence of microbiota on infantile colic has been investigated by means of stool studies[60] and on the effect of intrapartum[61] or neonatal antibiotic treatment.[62] These studies show an increased risk of infantile colic for children who were administered antibiotics at birth or in the first week. It is widely recognized that antibiotic treatment modifies the gut and vaginal microbiota, and a review by Zeevenhooven et al[63] studying children with colic identified a lower diversity in their intestinal microbiota, an abundance of microorganisms such as *Escherichia, Enterobacter*, and *Klebsiella* and a delayed or altered colonization by *Lactobacillus* spp. It has been demonstrated that *Lactobacillus* spp. has a protective effect against gas production bacteria such as *Escherichia, Enterobacter*, and *Klebsiella*.[64] Recently, studies have also highlighted the presence of fecal calprotectin in stool samples from children suffering from infantile colic.[60] Fecal calprotectin is a biochemical marker that indicates the presence of inflammation in the intestinal tract. Higher levels of IL-8, MCP-1, and MIP-1β have also been found in blood samples of colicky children, suggesting low grade systemic inflammation.[65]

Factors influencing the microbiota of children and their mothers have thus been widely explored by researchers, with particular attention paid to maternal medical and psychological status. Maternal health conditions such as obesity,[66] migraine,[66] tobacco consumption,[67] anxiety,[68] and depression represent risk factors for infantile colic. Paternal support to the expectant mothers,[69] familial support and a couple's level of happiness have also been linked to a lower risk of infantile colic. Moreover, paternal depression has been linked to infantile colic.[70]

The complexity of infantile colic is also influenced by an immature CNS. Indeed, the prevalence and the intensity of infantile colic decreases at around 8 weeks of age, which corresponds to the transition from reflex mechanisms to behavior controlled by the cerebral cortex.[63] A perfect example of the effects of CNS immaturity is the preterm population where the risk of infantile colic is increased, and some studies have shown that increased prevalence corresponds with the degree of prematurity.[71] Similarly, newborns with a lower birth weight tend to suffer more with colic.[72] The immature enteric nervous system may contribute to infantile colic by way of gut dysmotility, which leads to altered mucus secretion and modification of microbial composition.

Although the pathophysiology of infantile colic is complex, there is a better understanding of the outlook for children with colic. In follow-up studies of children between 5 years old[73] and 10 years old,[74] an increase in sleep disorders, aggression or anger, and ADHD have been observed.[75] Concerning somatic health problems, infantile colic has now been linked to recurrent abdominal pain[74] and migraine[29,30,76,77] in numerous studies. The first case report linking migraine to infantile colic was published by Katerji and Painter[78] in 1994 and describes an infantile migraine presenting as colic. In 2013, a case-control study of 679 patients showed that children with migraine were more likely to have experienced infantile colic (OR, 6.61; CI 95%, 4.38-10.00; $P < 0.001$)[77] and other study has reached the same conclusion.[76] This hypothesis has been strengthened by studies linking parental migraine to infantile colic,[79] allowing us to consider the possibility that these phenomena are symptoms on the same spectrum.[29,80]

Concerning the treatment of infantile colic, it has been at an impasse for many years. A recent systematic review from Hjern et al[81] found moderate evidence to support the efficacy of *Lactobacillus reuteri* DSM 17 938 in the treatment of infantile colic (favorable out-

come in 3 out of 4 randomized control trials). On the other hand, Hjern et al[81] reported that dietary modification (formula enriched with Lactobacillus) failed to show improvement of symptoms.

Functional Abdominal Pain Disorders Associated With Migraine

The Rome IV classification categorizes the functional gastrointestinal disorders (FGID) in children into 3 subtypes: (1) functional abdominal pain disorders, (2) functional nausea and vomiting disorders, and (3) functional defecation disorders.[32]

There are 3 subtypes of functional abdominal pain disorders: IBS, FD, and AM. Here we are interested in IBS and FD as they are the only 2 that studies have shown as being linked to migraine.[13,14,16] They are not considered as abdominal variants of migraine, in comparison to AM, in the ICHD-3b as, so far as is known, they coexist with migraine, without being temporarily linked to it. The most frequent FGID identified in toddlers is functional constipation[82] which is part of the functional defecation disorders, but again with no link to migraine proven to date.

Irritable Bowel Syndrome

The Rome IV classification[32] defines IBS in children as: (1) abdominal pain in at least 4 days per month associated with 1 or more of the following: (a) related to defecation, (b) a change in frequency of stool, and (c) a change in form (appearance) of stool; (2) in children with constipation, the pain does not resolve with resolution of the constipation (in this case, the child has functional constipation); and (3) after appropriate evaluation, the symptoms cannot be fully explained by other medical conditions.

IBS can be divided into subtypes reflecting the predominant stool pattern: IBS with constipation, IBS with diarrhea, IBS with constipation and diarrhea, and unspecified IBS.

According to a meta-analysis of 16 studies on the prevalence of IBS in Asian children, the prevalence ranges from 2.8% to 25.7% with a pooled prevalence of 12.4%.[83] The prevalence risk ratio for girls to boys is 1.39. The prevalence of IBS in children from the Mediterranean region of Europe is evaluated at 4.0%.[84]

IBS etiology is most likely multi-factorial involving biological, psychological, and social factors.[85] Visceral hyperalgesia (or hypersensitivity) and visceral hypervigilance are key concepts in current research on pathophysiological mechanisms of IBS.[86] Brain imaging studies show that the neural processing of visceral stimuli is altered in IBS.[85] There is also growing evidence to suggest that peripheral immune mechanisms and disturbed neuro-immune communication could play a role in the pathophysiology of visceral hyperalgesia. The contribution of both stress and negative emotions on symptom frequency and severity has been studied for some time now amongst children.[87] As a gut-brain axis disorder, the influence of microbiota has also been studied in IBS and Hollister et al[88] observed a significant difference in bacterial species (*Flavonifractor plautii* and *Lachnospiraceae bacterium* 7_1_58FAA) in IBS cases compared to control patients. Using artificial intelligence programming, Hollister et al[88] manage to distinguish stool features that could help diagnose IBS. The neuroimmune system, an element of the gut-brain axis, has also been explored and found to be activated in children suffering from IBS. Increased fecal granins in the stool,[89] increased gut permeability,[90,91] and increased serum brain-derived neurotrophic factor (BDNF) and proBDNF have been highlighted recently in pediatric studies.

The relationship between food allergies and recurrent abdominal pain, IBS in particular, has also been widely explored.[92] Some studies have shown an improvement in the severity and the frequency of pain in pediatric patients under fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) exclusive-regime.[93] In addition, the role of food on their symptoms is often expressed by IBS patients, whether they are adults or children.[94]

The role of personal beliefs and psychological factors is proven to impact the severity of symptoms. The transmission of somatic symptoms inside the family nucleus is part of the difficulty in acknowledging the symptoms of IBS patients, as shown by van Tilburg et al[95] with mothers and fathers of IBS patients also tending to report more symptoms concerning themselves.[96] The presence of adverse life events, inducing fear, increases the risk of IBS symptoms presenting in children.[97] Thus, anxiety and depression are predictors of abdominal pain severity in IBS patients.[87] In some families, the secondary benefit of having abdominal pain, such as providing an excuse to avoid household tasks, increases the risk of IBS in low-birth-weight children.[98] These studies show the difficulties in understanding the underlying causes of such a multi-factorial syndrome.

The treatment of IBS in children is still mostly dominated by non-pharmaceutical interventions such as parental education, diet (FODMAP exclusion, gluten free or increase of fiber consumption) or behavioral therapy. Unfortunately, most of the trials regarding pharmaceutical therapies study children suffering from functional abdominal pain and not IBS or FD alone.[98-100] A lack of clear evidence makes it very difficult to prioritize 1 treatment over another among: antiemetics (domperidone), antidepressants (tricyclic

or selective serotonin reuptake inhibitors), acid suppressing agents, antispasmodics, and antihistamines. However, probiotics seem to be effective in treating IBS in children with an estimated number need to treat of 4 according to a meta-analysis of 19 randomized control trials (RCTs).[101]

Regarding the evolution of IBS in children, the majority (60%) will observe the disappearance of their symptoms over 2 years following the diagnosis, regardless of age, sex, and impact of symptoms.[102,103] As exposed previously for abdominal variants of migraine, the initial diagnosis of IBS increases the chance of a symptom's resolution, which makes the positive diagnosis a very important step in the support of IBS patients.[21] Le Gal et al[16] showed a 3.47 OR (95% CI, 1.81-6.62; $P = 0.0002$) of IBS in child migraineurs in a retrospective case-control study of 1072 patients. Retrospective and prevalence studies that were interested in the prevalence of IBS and FGID in adult and children migraineurs show an important correlation between these 2 disorders.[13-16,104] In a large United States IBS cohort of 97 000 patients a 60% higher odds of migraine was demonstrated in the IBS population compared to control patients in an adult population.[15] In the adult population, the symptoms are the same as defined for children in the Rome IV classification. In a recent review on the prevalence of IBS in adults, the Rome Foundation refuses to give a pooled percentage for IBS since the mean prevalence in individual countries ranged from 1.1% (France and Iran) to 35.5% (Mexico).[105] To shed light on the pathophysiology of IBS studies focusing on regional and cross-cultural differences are needed.

Functional Dyspepsia

The diagnosis criteria for FD in children, as defined by the Rome IV classification,[32] must include one or more of the following symptoms at least 4 days per month: (1) postprandial fullness, (2) early satiation, (3) epigastric pain or burning not associated with defecation, and (4) after appropriate evaluation the symptoms cannot be fully explained by other medical conditions.

Within FD, we describe 2 subtypes[32]: postprandial distress syndrome and epigastric pain syndrome. The postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal, which can be associated with abdominal bloating, postprandial nausea, or excessive belching. The epigastric pain syndrome is defined as bothersome pain or burning localized to the epigastrium, without a retrosternal component and the ingestion of a meal being a trigger or an improvement factor. As for previous exposed syndromes, the diagnosis of FD requires clinical examination and history only. However, FD and gastroesophageal reflux can be difficult to distinguish, so the requirement of esophagogastroduodenoscopy in the diagnosis of FD has been debated.[106] The Rome IV classification considers there is no compelling evidence to require an esophagogastroduodenoscopy in order to make a diagnosis of FD in the pediatric population.[32]

The prevalence of FD is described around 7.6%[107] of children, using the Rome IV diagnostic criteria.

Concerning FD in the adult population, a recent review by Wauters et al[108] consider it as the most common functional upper gastrointestinal disorder affecting 15% of the general population. Its symptoms do not differ in the Rome IV classification for either adults or children.

The pathophysiology of FD still remains unclear. It is a complex combination of physiologic, genetic, environmental, and psychological factors.[109] We can distinguish 2 major mechanisms: gastric motility abnormalities and impaired gastric accommodation and visceral hypersensitivity.[110] Gastric accommodation is defined by the ability of the stomach to distend appropriately during a meal with an increase in gastric volume in the absence of increased gastric pressure. Gastric motility can be explored by a number of different methods (sodium acetate breath tests,[111] gastric emptying scintigraphy,[112] or electrogastrography[113] for example) and can be compared in FD and control patients in the pediatric and adult populations. Studies have shown delayed gastric emptying,[111,112] antral hypomotility,[113] and a negative correlation between gastric emptying rate and severity of abdominal pain[114] among dyspeptic patients. This impaired accommodation may be linked to abnormalities of the vagal reflex and intrinsic inhibitory innervation.[115] Studies on adults and children highlighted abnormal gastric sensorimotor function.[116] The visceral hypersensitivity to gastric distention in FD can be considered as a model of a gut-brain axis disorder. The presence of inflammatory cells (eosinophilia and high mast cell density) can be found in the stomach and duodenum of children suffering from FD,[117] especially if they are also suffering from headaches.[118] An altered intestinal permeability, as observed in IBS or AM, was not observed in FD patients.[119] The role of *Helicobacter pylori* on FD and migraine has also been studied. In 2016, a meta-analysis of 25 RCT and 5555 adult patients with FD showed a 1.23-fold improvement of symptoms after *H. Pylori*'s eradication at long-term follow-up.[120] Moreover, a cohort of 305 adult dyspeptic patients showed a significantly positive association between *H. Pylori* and migraine and family history of headache.[121] Concerning treatment, in the pediatric population, a systematic review of three RCTs studying pharmaceutical options to treat FD found no evidence to support the use of pharmacological drugs.[122]

An important intrinsic role for psychosocial factors and psychiatric disorders, especially anxiety and depression, has been described in the etiopathogenesis of FD, in addition to their putative influence on health care-seeking behavior. Around 50% of FD patients show high anxiety score responses.[119]

Finally, for a few years, studies have underlined a link between FD (postprandial distress syndrome or epigastric pain syndrome) and migraine in the pediatric population. Di Stefano et al[123] were interested in the prevalence and pathophysiology of migraine in functional dyspeptic adult patients and demonstrated 54% of epigastric pain syndrome patients and 76% of postprandial distress syndrome patients also suffered from migraine. Among the postprandial distress syndrome patients, the severity of fullness and early satiation correlated to the severity of migraine.[123] Cohort studies also showed an association between primary headache and FD: 25% of FD children declared having headache more than 3 times a month on an internet questionnaire survey,[124] 60% of adults migraineurs suffer from FD in a prevalence study,[125] and Lankarani et al[14] found a 1.68 OR ($P < 0.001$) for FD among 1038 adults migraineurs in Iran. Le Gal et al[16] calculated an odds ratio of 10 for FD among children suffering from migraine.

Conclusion

The aim of this review is to summarize the recent knowledge on abdominal variants of migraine and functional abdominal pain disorders associated to migraine, as they appear to be part of a wider spectrum of diseases now being explored as brain-gut disorders (Table 2). Migraine and related syndromes have a great impact on the quality of life of children and their future as adults. The understanding of pathophysiological mechanisms underlying these conditions is crucial in order to improve diagnosis, treatment, and follow-up in these children.

In this review, we discussed whether the inflammatory mediators, gut microbiota profile, neuropeptides, serotonin pathway, stress hormones, and nutritional substances which are related with brain-gut axis could be a pathophysiology of abdominal variants of migraine and functional abdominal pain disorders associated to migraine. AM, CVS, infantile colic, and IBS appear to be mediated by neuroinflammatory and neuroimmune patterns that can also be found in migraine. For FD, alterations in motility and gastric accommodation are among the main hypotheses. Therefore, it is possible that alterations of the gut-brain axis could be involved in the underlying mechanism for all of the abdominal syndromes associated with migraine.

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