



Gastrointestinal disorders associated with migraine: A comprehensive review

Carlos R Cámara-Lemarroy, Rene Rodriguez-Gutierrez, Roberto Monreal-Robles, Alejandro Marfil-Rivera

Carlos R Cámara-Lemarroy, Alejandro Marfil-Rivera, Servicio de Neurología, Hospital Universitario “Dr. José E. González”, Universidad Autónoma de Nuevo León, Monterrey 64460, México

Rene Rodriguez-Gutierrez, Servicio de Endocrinología, Hospital Universitario “Dr. José E. González”, Universidad Autónoma de Nuevo León, Monterrey 64460, México

Roberto Monreal-Robles, Servicio de Gastroenterología, Hospital Universitario “Dr. José E. González”, Universidad Autónoma de Nuevo León, Monterrey 64460, México

Author contributions: Cámara-Lemarroy CR led the conception and review of the literature, and drafted the manuscript; Rodríguez-Gutierrez R and Monreal-Robles R helped gather the literature for review and in preparing tables and figures; Marfil-Rivera A helped draft the manuscript and approved the final version; all authors reviewed the manuscript for important intellectual content and participated in the final approval of the version to be published.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Carlos R Cámara Lemarroy, MD, Servicio de Neurología, Hospital Universitario “Dr. José E. González”, Universidad Autónoma de Nuevo León. Monterrey, México. Ave. Madero y Gonzalitos s/n, Monterrey 64460, México. rcamara83@hotmail.com
Telephone: +52-81-83337798
Fax: +52-81-83337798

Received: May 30, 2016

Peer-review started: May 30, 2016

First decision: July 12, 2016

Revised: August 3, 2016

Accepted: August 23, 2016

Article in press: August 23, 2016

Published online: September 28, 2016

Abstract

Migraine is a recurrent and commonly disabling primary headache disorder that affects over 17% of women and 5%-8% of men. Migraine susceptibility is multifactorial with genetic, hormonal and environmental factors all playing an important role. The physiopathology of migraine is complex and still not fully understood. Many different neuropeptides, neurotransmitters and brain pathways have been implicated. In connection with the myriad mechanisms and pathways implicated in migraine, a variety of multisystemic comorbidities (*e.g.*, cardiovascular, psychiatric and other neurological conditions) have been found to be closely associated with migraine. Recent reports demonstrate an increased frequency of gastrointestinal (GI) disorders in patients with migraine compared with the general population. *Helicobacter pylori* infection, irritable bowel syndrome, gastroparesis, hepatobiliary disorders, celiac disease and alterations in the microbiota have been linked to the occurrence of migraine. Several mechanisms involving the gut-brain axis, such as a chronic inflammatory response with inflammatory and vasoactive mediators passing to the circulatory system, intestinal microbiota modulation of the enteric immunological milieu and dysfunction of the autonomic and enteric nervous system, have been postulated to explain these associations. However, the precise mechanisms and pathways related to the gut-brain axis in migraine need to be fully elucidated. In this review, we survey the available literature linking migraine with GI disorders. We discuss the possible physiopathological mechanisms, and clinical

implications as well as several future areas of interest for research.

Key words: Migraine; Headache; Microbiota; Review; Gastrointestinal diseases

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Migraine is a recurrent and disabling primary headache disorder that commonly affects a significant proportion of the global population. Recent reports demonstrate an increased frequency of gastrointestinal (GI) disorders in patients with migraine compared with the general population. We review the available literature linking migraine with GI complications and comorbidities.

Cámara-Lemarroy CR, Rodriguez-Gutierrez R, Monreal-Robles R, Marfil-Rivera A. Gastrointestinal disorders associated with migraine: A comprehensive review. *World J Gastroenterol* 2016; 22(36): 8149-8160 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i36/8149.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i36.8149>

INTRODUCTION

Migraine is a disabling primary headache disorder, defined by the International Classification of Headache Disorders as recurrent, moderate to severe headache attacks lasting 4-72 h with associated features including nausea and/or vomiting^[1] that affects over 17% of women and 5%-8% of men^[2,3]. Recent publications have suggested that its worldwide prevalence may surpass 20%, and that it consistently rates as one of the most disabling conditions^[4]. The subtype of chronic migraine affects up to 2%-5% of the population worldwide^[5,6].

Susceptibility to migraine is thought to be multifactorial, with genetic hormonal and environmental factors all playing an important role. Unbiased genome-wide association studies have identified 13 migraine-associated variants pointing at genes that cluster in pathways for glutamatergic neurotransmission, synaptic function, pain sensing, metalloproteinases and vasculature^[7]. The physiopathology of migraine is complex and the precise mechanisms and pathways involved remain to be fully elucidated. Many different neuropeptides, neurotransmitters and brain pathways have been implicated, but whether pain generates in central or peripheral structures is a matter of debate. A review of all of these mechanisms is beyond the scope of this article, and excellent recent papers by Nosedá *et al.*^[8] and Burstein *et al.*^[9] thoroughly summarize the current concepts of migraine physiopathology.

Briefly, sequential steps of neurogenic inflammation, peripheral trigeminovascular input, and central cortico-

trigeminal nuclei activation are thought to mediate migraine pathogenesis. Headache arises initially from an inflammatory response in the dura, mediated by vasoactive peptides, including calcitonin gene-related peptide (CGRP), substance P and neurokinin A. These are all released by trigeminal fibers and lead to activation of nociceptive perivascular sensory nerve terminals located in the meningeal vasculature^[8]. Perpetuation of headache is thought to be secondary to increased cortical responsiveness, while cortical spreading depression (CSD) has been hypothesized to represent the pathophysiological correlate not only for crisis onset but also for migraine aura.

The many stages of migraine headache from prodromal to postictal symptoms involve alterations in multiple cortical and subcortical structures. CSD itself can also activate the trigeminovascular system. Nociceptive input from trigeminal fibers converge onto the spinal trigeminal nucleus, which later modulates the activity of second-order structures such as the ventrolateral area of the upper cervical and medullary dorsal horn, the periaqueductal gray matter, rostral trigeminal spinal nuclei, brainstem reticular areas, superior salivatory nuclei and the cuneiform nuclei^[8,9]. Activity in these brain regions modulates the myriad of symptoms that follow migraine headache. The frequency of accompanying autonomic symptoms, such as nausea, vasoconstriction, vasodilation and diaphoresis as well as the participation of the hypothalamus, has led some investigators to propose that autonomic dysfunction may also play an important part in migraine pathophysiology.

It is widely known that migraine is associated with a variety of comorbidities, mainly cardiovascular, psychiatric and other neurological conditions. Hypertension, hyperlipidemia, sinusitis, asthma, pulmonary emphysema, insomnia, affective disorders and fibromyalgia have all been associated with migraine. Recent studies have found that gastrointestinal (GI) disorders also appear to be more frequent in patients with migraine (PWM) than in the general population^[10]. In this review, we survey the available literature linking migraine with GI complications and comorbidities.

HELICOBACTER PYLORI INFECTION

Interest in a possible association between *Helicobacter pylori* (*H. pylori*) infection (the most relevant cause of gastritis and peptic ulcer) and migraine first arose after this microorganism was recognized as the cause of myriad extra digestive manifestations, including neurological diseases^[11,12]. Its association with both cardiovascular (including typical functional vascular disorders such as primary Raynaud phenomenon) and autoimmune diseases has been established, possibly due to a chronic inflammatory response with local secretion to the circulatory system of numerous inflammatory and vasoactive mediators^[11,12]. Both vascular and inflammatory hypotheses have been proposed

as mechanisms mediating migraine physiopathology, making a link between *H. pylori* and migraine at least plausible enough to warrant investigation.

The evidence for a possible association between *H. pylori* infection and migraine is surrounded by some controversy. In one study^[13], investigators performed endoscopic procedures in 31 children with migraine and abdominal complaints and found a remarkably high prevalence of esophagitis (41.9%), corpus gastritis (51.6%), antral gastritis (38.7%) and duodenitis (87.1%). However, only 7 had *H. pylori*, thus failing to support an association between *H. pylori* and migraine.

A study assessing 200 subjects affected by primary headache found a *H. pylori* infection prevalence of 40%. It also found a higher prevalence of migraine without aura in infected patients^[14]. A similar study performed on 225 PWM found that 40% were colonized by *H. pylori*, and that the intensity, duration and frequency of migraine attacks were significantly reduced in all patients who underwent *H. pylori* eradication^[15]. These results were questioned by a later case-control study of 103 PWM and 103 control subjects, in whom the proportion of *H. pylori* infection was almost identical; in addition, there were no clinical or demographic differences between colonized and non-colonized migraine patients^[16]. In a follow-up of the former study^[17], 175 PWM were compared with 152 matched controls and investigators found no difference in prevalence of infection (40% vs 39%, respectively). However, among infected subjects, they found a significantly higher prevalence of CagA-positive strains in patients affected by migraine with aura compared with those affected by migraine without aura (41% vs 19%) and with controls (41% vs 17%), suggesting a pathogenic role for that specific strain of *H. pylori*. In contrast, a group of Turkish investigators compared the prevalence of *H. pylori* infection in 70 PWM and found a greater prevalence when compared to 60 matched controls, as well as a slight clinical benefit after eradication therapy^[18].

Besides different *H. pylori* strains, differences between migraine subtypes could also explain some of these inconsistent results. In a study on 49 PWM without aura, *H. pylori* infection was more prevalent compared to controls, and interestingly investigators also found much higher prevalence in PWM without family history or hormonal fluctuations, suggesting that *H. pylori* infection could be particularly relevant in patients with fewer known risk factors for migraine^[19]. However, an earlier study had reported that the association with *H. pylori* was exclusive for migraine with aura^[17]. In an attempt to resolve the controversy over the epidemiological association between migraine and *H. pylori*, a recent meta-analysis that included five studies and 903 patients found an overall *H. pylori* infection rate in PWM of 45%, compared to 33% in controls, with subgroup analysis finding greater infection rate of *H. pylori* in Asian patients compared to Europeans, but no difference among migraine

subtypes^[20]. Recently, a case-control study demonstrated higher IgM antibody titers against *H. pylori* in PWM compared to controls; also, they found a positive correlation between IgG antibody titers and severity of migraine^[21]. This suggests the importance of *H. pylori* active infection in migraine.

The previous epidemiological studies suggested that eradication therapy could be beneficial for migraine control, but in a non-controlled setting. In the only available double-blind, randomized, controlled clinical trial, 64 patients diagnosed with migraine-type headache were randomized to receive migraine treatment and *H. pylori* eradication treatment or migraine treatment and placebo^[22]. Using the Migraine Disability Assessment (MIDAS) questionnaire, on enrollment patients in the treatment group had more severe symptoms, but these differences disappeared after completing the study. Analysis of the change in MIDAS scores between baseline and completion of the study revealed a slight benefit for the treatment group.

As for possible pathophysiological mechanisms, few studies have made relevant findings. In small studies evaluating the redox state of PWM, *H. pylori* infection did not influence plasma accumulation of peroxidative substances, values of nitrite/nitrate concentrations or expression of systemic nitric oxide^[23,24]. Others have speculated that elevated levels of interleukin-10 might be implicated, considering that studies have shown elevations in this cytokine both in PWM as well as in patients with infection with *H. pylori*, particularly with CagA-positive strains^[25,26]. This has a therapeutic implication since the administration of sumatriptan (5-HT_{1D} receptor agonist) reduces the levels of interleukin-10 during a migraine attack^[26]. The serum levels of CGRP, which has been suggested as a biomarker for chronic migraine^[27], are also higher in those with *H. pylori*-associated duodenal ulcers compared with healthy controls^[28].

In conclusion, whereas epidemiological evidence appears to support an association between migraine and *H. pylori* infection, the data is limited and investigations should focus on subgroups of patients and of different ethnicities, and should consider the regional variations in *H. pylori* infection^[20]. Furthermore, intervention studies suggest a small benefit for eradication therapy, but the long-term benefit has not been established, and a possible intrinsic role for antibiotic or antacid treatment cannot be ruled out completely^[29]. Available studies are heterogeneous in both populations and treatments used, both in migraine control and *H. pylori* eradication.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS), considered a neuro-gastroenterologic functional disorder, shares some environmental risk factors with migraine (predominately affecting the female sex and younger individuals), and could be associated with conditions of smooth muscle

dysfunction. IBS is associated with a number of extra-intestinal manifestations, and both diseases are widely prevalent and share many somatic and psychiatric comorbidities^[30]. In systematic reviews of the existing literature on IBS and its comorbidities, patients were found to present a 2-fold increase in other somatic disorders, suggesting a common physiopathological mechanism^[31]. Indeed, chronic headache was reported in 34%-50% of all IBS patients^[31,32].

Large population-based studies of the prevalence of IBS and accompanying symptoms show migraine, as well as heartburn, dyspepsia, flushing, palpitations and urinary symptoms, to be more common in patients with IBS^[33]. Specifically, out of 1620 subjects, 350 fulfilled criteria for IBS, and of these, 32% complained of migraine-type headache, compared with 18% in controls. Of course, within a population of PWM, comorbid constellations vary, differing in headache and psychosocial profiles, highlighting the heterogeneity of environmental and genetic factors^[34]. Nevertheless, an epidemiologic association has been since confirmed by various studies. In a cohort of 208 patients with IBS, 17% had migraine, compared to 8% in 1240 controls^[35]. A more recent cohort study investigating 97593 IBS patients exhibited a migraine prevalence of 6%, compared to 2.2% in healthy controls^[36]. A migraine cohort of 14117 newly-diagnosed patients presented similar results, with an adjusted incidence of IBS 1.95-fold higher than in controls (73.87 vs 30.14 per 10000 person-years), particularly in those under 30 years of age^[37].

There is some indication that comorbid headache disorders in IBS patients could negatively alter their clinical course. In a study of IBS patients comparing first-time attendees with chronic attendees to an outpatient clinic, 40% of first-time attendees complained of mild headache and 1% of severe headache, compared to 59% and 23% of the chronic attendees, respectively^[38].

In a prospectively identified, hospital-wide population of migraine patients, another study found that 70% of patients met the Rome III criteria for concurrent functional gastrointestinal disorders (FGID), with 40.4% meeting criteria for IBS^[39]. The authors also demonstrated a clear link between coexistent FGID symptoms, psychological comorbidity and worse scores in anxiety/depression scales.

In the search for a common pathogenetic mechanism for IBS and migraine, neuroendocrine factors, immunological factors, the brain-gut axis and even the intestinal microbiota have been postulated^[30]. A role for serotonin (5-HT) has been postulated in both diseases, as well as for other factors such as biopsychosocial dysfunction, heredity, genetic polymorphism, central/visceral hypersensitivity, somatic/cutaneous allodynia and the neurolimbic pain network^[30]. Another possible physiopathologic link could be derived from treatment studies. A recent small, clinical study, showed that an IgG-based food elimination diet could reduce

symptomatology and attack prevalence of both disorders in patients with comorbid IBS and migraine^[40].

GASTROPARESIS

Gastroparesis can be defined as delayed emptying of the stomach in the absence of mechanical obstruction, and its clinical manifestations include nausea, vomiting, bloating and weight loss, among other symptoms^[41]. An association between migraine and alterations in gastric motility has been noted, describing this motility disorder as a stomach with a functional "vagotomy"^[42]. A delay in gastric emptying time and increased pyloric tone characterized these alterations. The recognition of GI stasis in PWM led to initial concerns on the absorption of analgesics and the effect on therapeutic efficacy, but some authors emphasized the accentuation of overall distress and inconvenience caused by GI symptoms^[43]. Studies confirmed an effect of gastric emptying delay time over the absorption of paracetamol and acetylsalicylic acid, among other common analgesics^[44]. One study established the close association of gastroparesis with migraine attacks. PWM during a pain-free period showed normal gastric emptying times measured with an epigastric impedance method, but these times were significantly delayed during severe or moderate attacks, and delay times were significantly correlated with the intensity of headache, nausea and photophobia^[45].

The physiology of emesis during migraine attacks could, in some manner, mirror those of gastroparesis, and these considerations have had therapeutic implications, as both dopaminergic and 5-HT₄ agonists have prokinetic properties^[46]. Early findings of an apparently normal gastric motility outside of migraine attacks^[45] suggested that the physiopathology of gastroparesis in migraine was mediated by pain mechanisms, such as adrenergic and endogenous opiates, or to factors shared with the pathophysiology of a migraine attack itself. An excessive sympathetic response coupled with a decreased parasympathetic tone has also been postulated^[43]. However, a recent study with gastric scintigraphy showed that gastric emptying time is delayed in both ictal and interictal periods, suggesting an alteration in enteric autonomic function^[41,47]. Another study showed that PWM have meal-induced hypersensitivity of the stomach, due to a low postprandial discomfort threshold, irrespective of the presence of dyspepsia^[48].

More recent studies have further characterized migraine-associated gastroparesis, but these have also questioned the existence of an alteration outside the ictal period. Using gastric scintigraphy in 3 PWM, investigators found that gastric emptying delay occurs not only in ictal and interictal periods, but also in both drug-induced and spontaneous migraine attacks^[49]. However, other groups using similar methods were

not able to find differences in emptying time between patients without migraine and PWM in the interictal period^[50]. Of note, both studies included a very small sample, and only the latter included an age- and sex-matched control group. In a larger gastric scintigraphy study, involving 27 PWM and 12 healthy controls, again there was no gastric emptying delay interictally^[51]. However, in this study, PWM who experienced other GI symptoms were excluded. The controversy over this issue also stems from methodological issues, such as the criteria used to define gastric emptying delay, which should be adapted to the specific population studied, as well as small sample sizes and inadequate control group selection^[52].

Although there is enough evidence to link gastroparesis with migraine, the nature, causes, correlates and consequences of gastric stasis in migraine are just beginning to be elucidated^[41,53]. There is controversy over whether gastroparesis occurs both ICTALLY and interictally, but it is clear that it is associated with increased discomfort and affects the effectiveness and absorption of orally administered drugs. This suggests that non-oral formulations of commonly used migraine medications as well as the addition of prokinetic drugs could theoretically offer an advantage^[41]. At least one small trial showed an additive effect of a prokinetic drug (trimebutine) over the efficacy of rizatriptan, a 5-HT_{1B/1D} agonist^[54].

OTHER FUNCTIONAL GI DISORDERS

Other functional GI disorders have been linked to primary headaches, but there is doubt as to a specific link with migraine. In population-wide registries, both diarrhea and constipation are significantly more frequent in headache sufferers compared to the general population, with no apparent difference between PWM and non-PWM^[10]. In a cross-sectional study of 326 children, nearly 20% of those who complained of headaches had constipation, a significantly higher number than in controls^[55]. However, no such association was found among PWM. Another retrospective study of 96 patients with primary headache also found comorbid constipation in 25%, but this was mostly associated with tension-type headaches^[56]. All studies reported a close correlation of constipation with headache severity, suggesting that it is this factor, together with the related affective and emotional distress, that more adequately explains the association. In a well-designed web-based survey aiming to screen for symptoms of reflux, among 1832 PWM, 22% reported having the diagnosis of GERD, 11.6% reported experiencing heartburn, and 15.8% reported undiagnosed reflux symptoms^[57]. The most common used medications were triptans but a significant number used NSAIDs. Whether reflux symptoms are a side effect of these medications or are independently associated with migraine is unknown.

HEPATO-BILIARY DISORDERS

There is little evidence linking migraine with hepatobiliary disorders. In a community study on the prevalence of chronic complaints, migraine and some types of biliary colic or right upper abdominal quadrant discomfort occurred together with some regularity, but a statistical association was not established^[58]. In another study, 488 healthy patients and 99 migraine patients reported upper abdominal symptoms, including unexplained right upper quadrant discomfort. These symptoms were more than twice as frequent in PWM, after adjusting for age, sex, smoking and consumption of analgesics and alcohol^[59]. A study of twin samples including a cohort of 1200 patients, found an association between migraine and biliary tract disorders, with higher ORs in monozygotic twins (OR = 3.5) than in dizygotic twins (OR = 1.7-2.7)^[60]. Waist circumference and female sex were also associated with migraine, but the association with biliary tract disorders remained even after controlling for these factors. The stronger association in monozygotic twins suggests a genetic influence. A weakness of the study was that the migraine diagnosis was based on iterated questionnaires and personal interviews and not guideline-based criteria.

As with other functional GI disorders, such as IBS, functional biliary tract disorders would be expected to be more robustly represented in PWM. In a recent study involving 972 patients with biliary dyskinesia (over 80% women), 14.6% were PWM^[61], a proportion similar to worldwide prevalence^[4,62]. In this study, 30% of the cohort presented comorbid anxiety or depression as well. Interestingly, migraine was an independent predictor (OR = 2.13) for continued medical resource utilization (for recurrent attacks of biliary symptoms), which could suggest a more severe course in PWM.

In experimental studies, cholecystokinin (CCK) coexists with CGRP in the trigeminal ganglion; and trigeminal ganglion stimulation was able to induce local increases of CCK^[63]. CGRP is also able to influence biliary motility *in vitro*, and impaired CGRP release is associated to biliary tract disease in humans^[64,65]. This evidence is proposed as a possible common physiopathologic mechanism linking biliary tract disorders and migraine, in addition to a possible role of obesity and female hormones and a vasodilatory effect of CCK^[60,66].

An association between liver disease and migraine and other headache types is even rarer and of dubious physiopathological standing^[67]. A recent cross-sectional study showed that migraine patients with non-alcoholic fatty liver disease (NAFLD) had significantly more attacks and a higher frequency of auras, but also higher waist circumferences and metabolic disturbances^[68]. The study was not designed to establish an independent association of NAFLD and migraine, but did suggest a more aggressive disease with a simultaneous diagnosis. Obesity and metabolic

disturbances, which are important determinants of NAFLD, are also associated with an increased risk of migraine^[69,70].

Based on the available data, CCK, which seems to have a role in the physiopathology mechanism in migraine^[60,63,66], is released in response to fatty acids in the proximal intestine^[71,72]. In this respect, a cross-over study including 83 PWM randomly assigned to a low lipid diet or a normal lipid diet found that the number (2.9 ± 3.7 vs 6.8 ± 7.5 , $P < 0.001$) and severity [1 pt indicated mild, 2 pts moderate and 3 pts very severe headache (1.2 ± 0.9 vs 1.7 ± 0.9 , $P < 0.01$)] of migraine attacks significantly decreased during the low lipid diet intervention periods^[73]. Likewise, a cross-sectional study showed that after a weight loss program, those who achieved a significant weight loss and metabolic control presented improvement of migraine^[70].

CELIAC DISEASE

Celiac disease (CD) is an autoimmune condition that occurs in those genetically predisposed to dietary gluten hypersensitivity, affecting about 1% of the general population^[74]. Besides GI symptoms, it is now known to have systemic involvement. Neurological complications are well-known manifestations of CD, including epilepsy, occipital calcification and migraine-like headaches; also, celiac antibodies have been described in patients with a wide range of neurological disorders, including encephalopathy, ataxia, neuropathy and myopathy, among others^[75]. Nonetheless, it remains unclear whether gluten sensitivity contributes to the pathogenesis of these disorders or whether it represents an epiphenomenon. Moreover, case reports of patients with concomitant CD and migraine describe the total disappearance of headaches after treatment of CD, and others describe particular combinations of signs and symptoms, such as CD, cerebral calcifications and migraine^[76,77], suggesting the existence of a pathophysiological association. Other single-case reports have described migraine as the presenting symptom in patients later confirmed to have CD^[78].

The search for antibodies associated with CD in migraine patients aims at establishing an epidemiological and possibly a physiopathological association. In an early study on the association between celiac antibodies and children with neurological disorders, including migraine, epilepsy and hypotonia, among others, investigators found only 13% of cases of anti-gliadin IgG antibodies and no cases of endomysial antibodies^[79]. Cases were not followed up with biopsies, but none seemed to have clinically evident CD. Another study involving 25 PWM (ages: 14-37; 22 females) did not find a single case of anti-gliadin antibodies in peripheral blood samples^[80]. However, the limitation of anti-gliadin antibodies is its low diagnostic accuracy; these antibodies have a high prevalence in normal population^[81]. Therefore, the reported association

between CD and migraine using this test may reflect a sampling error. In a more recent study of 100 children with migraine, only 2% had serologic tests positive for CD antibodies, a finding not different from a control group of 1500 healthy subjects^[82]. The only positive study, which included 73 children with migraine, found that 5.5% of patients have positive celiac antibodies compared with 0.6% in the control group^[83]. However, most of the seropositive children had normal duodenal biopsies, putting in doubt the diagnosis of CD. On the other hand, only 1 patient out of 147 controls was seropositive, a prevalence lower than what would be expected in the general population. Together, this data does not support screening for CD antibodies in PWM, but does not exclude a causal link in those affected with both disorders simultaneously.

The occurrence of few cases of CD in PWM and the high frequency of headaches in CD provide some support for a possible asymmetrical association. In a study of 72 adult patients with biopsy-proven CD who were screened for neurological disorders, 28% had migraine, among other neurological symptoms^[84]. A recent study of 188 patients with proven CD found that they had a significantly higher prevalence of migraine headaches compared with controls (OR = 3.79), particularly in women and those under 65 years of age^[85]. Additionally, there was a trend of more severe headaches in CD patients compared with controls. In a retrospective study of 354 children with CD, 24.8% had experienced headaches, compared to 8% in an age and sex-matched control group^[86]. The screening for migraine in patients with CD would, therefore, seem to be justified.

The occurrence of more severe headaches in patients with CD and migraine raises the question of a possible therapeutic effect of a gluten-free diet. In a study of 4 PWM and serologically and endoscopically confirmed CD, a gluten-free diet resulted in complete remission of migraine symptoms in one patient and improvement in frequency, duration, and intensity of migraine in the other 3^[87]. These improvements were associated with a reduction in single photon emission CT regional baseline brain tracer uptake in all 4 patients. Of note, these 4 patients were screened out of a population of 90 PWM (less than 5%). In another study of a cohort of Italian patients with CD, migraine-type headaches were more common than in controls (32%) and subsided partially with gluten-free diet^[88]. Other large cohorts of CD patients have similarly described improvement in migraine-type headaches with dietary intervention^[86,89].

Although the link between CD and migraine is not fully elucidated, they do share many psychosocial and pathophysiological characteristics. A physiopathological link is suggested by imaging studies. In a case series of 10 patients with CD and episodic headaches, brain MRI showed diffuse and heterogeneous hyperintensities involving white matter, similar to lesions described in PWM^[90]. The majority of those patients had symptom

Table 1 Summary of gastrointestinal disorders associated with migraine

GI disorder	Association	Proposed implicated mechanism	Clinical implication
<i>H. pylori</i> infection	Infection rate of <i>H. pylori</i> : 45% in PWM <i>vs</i> 33% in controls ^[20] Main affected: CagA-positive strains ^[17] Asian > Europeans ^[20]	Chronic inflammatory response with inflammatory and vasoactive mediators passing to the circulatory system ↑ Interleukin-10 (CagA-positive strains) ^[25] ↑ CGRP ^[28]	Screening of <i>H. pylori</i> infection in patient with migraine Improvement of migraine with <i>H. pylori</i> eradication ^[17,18,22]
Irritable bowel syndrome	6%-32% migraine-type headache in IBS patients <i>vs</i> 2.2%-18% in controls ^[33,35,36]	The brain-gut axis and the intestinal microbiota have been postulated ^[30,95] Serotonin, biopsychosocial dysfunction, heredity, genetic polymorphism, central/visceral hypersensitivity, somatic/cutaneous allodynia, neurolimbic pain network ^[30]	Improvement of migraine with elimination diet ^[40]
Gastroparesis	During a migraine attack gastric emptying delay and impairment of drug absorption has been demonstrated ^[44,45]	↑ Sympathetic response ^[43] ↓ Parasympathetic tone ^[43] Dysfunction of enteric autonomic system ^[41,47]	Increase absorption of antimigraine agents by administering antipaminergic and 5-HT4 agonists with antiemetic/prokinetic properties ^[46]
Hepato-biliary disorders	Association between migraine and biliary tract disorders ^[60] Genetic influence: In monozygotic pairs (OR = 3.5) In dizygotic pairs (OR = 1.7-2.7). Among the migraine characteristics, in those PWM with NAFLD, the presence of aura was higher (73.6% <i>vs</i> 26.5%), and the disease (9 yr <i>vs</i> 6 yr) and attack (72 h <i>vs</i> 48 h) durations were longer than in those without NAFLD ^[68] . Obesity and metabolic disturbances which are important determinants of NAFLD are also associated with an increased risk of migraine ^[69,70]	CCK has been found to coexist with CGRP in the trigeminal ganglion ^[63] . When stimulated induce local increase of CCK which has a vasodilatory effect ^[63,66] . CGRP has shown to influence biliary motility. The impaired CGRP release has been associated to biliary tract disease in humans ^[65]	Low-fat diet improves frequency and severity of migraine ^[73] In connection with NAFLD: Weight loss and metabolic control have shown to improve migraine ^[70]
Celiac disease	28% prevalence of migraine in subject with biopsy-proven CD ^[84] Higher prevalence of migraine in biopsy-proven CD group than in controls (21% <i>vs</i> 6%, OR = 3.79) ^[85] Main affected: Female Age < 65	Neurological complications in CD may be caused by a general inflammatory response ^[92] Elevated levels of interferon-gamma and TNF-alpha (both independently implicated in migraine and CD) modulate neuropeptide CGRP ^[93] .	The screening for migraine in patients with CD seems to be justified. Possible therapeutic effect with gluten-free diet ^[86-89]

GI: Gastrointestinal; PWM: Patients with migraine; CGRP: Calcitonin gene-related peptide; IBS: Irritable bowel syndrome; CCK: Cholecystokinin; NAFLD: Non-alcoholic fatty liver disease; CD: Celiac disease; TNF: Tumor necrosis factor.

improvement with a gluten-free diet. Authors have speculated that a state of hypervigilance, associated with an exaggerated response to future threats and episodic attacks, could transform a genetically sensitive nervous system into one susceptible to the alterations underlying these chronic and disabling diseases^[91]. Another hypothesis is that neurological complications in CD may be caused by a general inflammatory response, rather than be directly antibody-mediated. This idea is supported by a study that showed no correlation between neural antigens and neurologic symptoms in patients with CD^[92]. Hypothetically, elevated levels of interferon-gamma and tumor necrosis factor-alpha, both independently implicated in migraine and CD, and known to modulate the neuropeptide CGRP, could explain the apparition/progression of migraine symptoms in patients with CD^[93].

A summary of GI disorders associated with migraine,

proposed physiopathological mechanisms, and clinical implications is presented (Table 1).

MIGRAINE AND THE GUT MICROBIOME

There is evidence that suggests gut microbiota can modulate the brain-gut axis through many pathways, with a potential to influence brain function and nociceptive behavior^[94,95]. The intestinal surface contains 100 trillion microorganisms, separated from the host by a layer of columnar intestinal epithelial cells. Indirect links have been made between gut microbiota and the function of the major pathophysiological mechanisms associated with migraine: Serotonergic transmission, CGRP activity and cortical reactivity^[95]. Dysbiosis has an impact on immune function, epithelial barrier permeability, absorption and metabolism of nutrients affecting, in consequence, GI and central

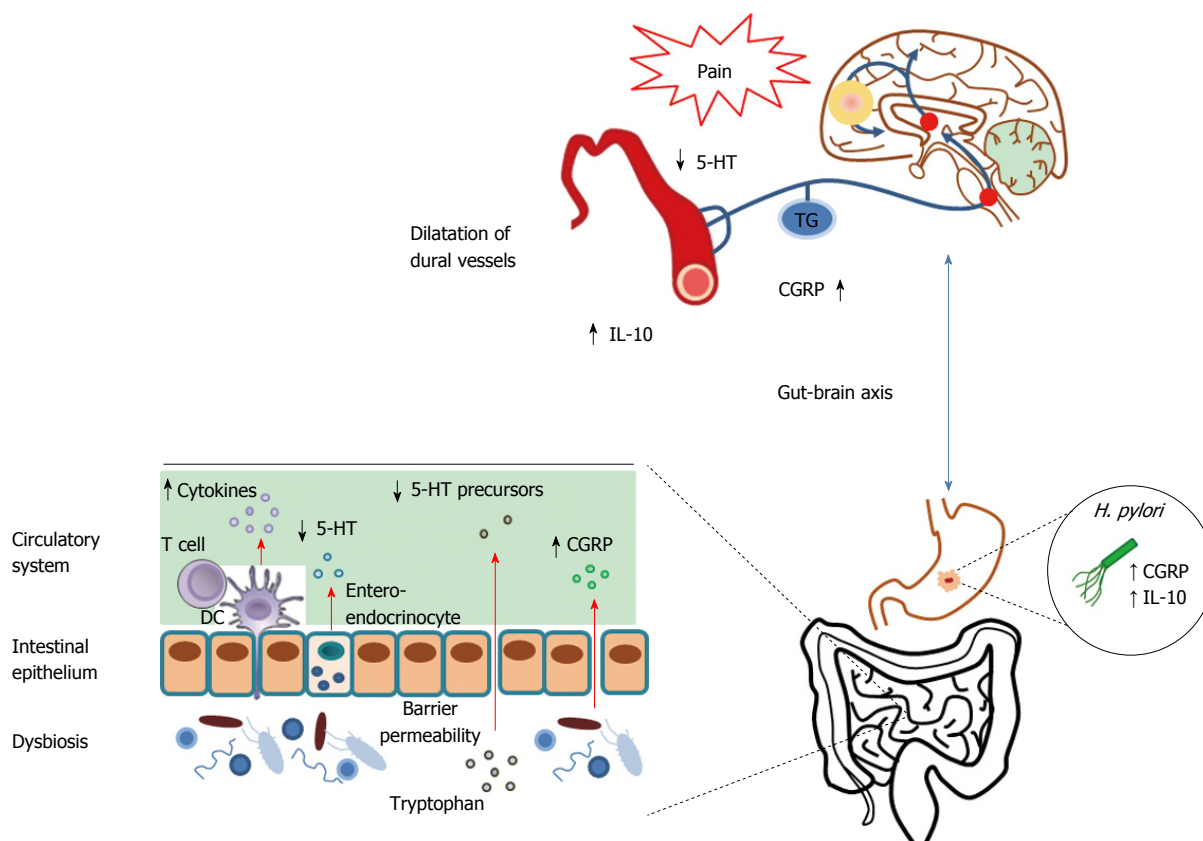


Figure 1 Role of the gut microbiota in migraine. Immunological, endocrine, metabolic and neural signals are important pathways by which the gut microbiota influences brain functions. Altered gut microbiota (dysbiosis) affects the normal assimilation of nutrients (tryptophan metabolism), barrier permeability, mucosal immune and enteroendocrine cells, affecting in turn some communication pathways; this results in the production of gut peptides (\uparrow CGRP) by certain microbes, abnormal release of cytokines (\uparrow IL-10) and hormones (\downarrow 5-HT). *H. pylori* also plays a role in the release of cytokines (IL-10) and CGRP. The increased cytokines and CGRP levels, as well as the decreased 5-HT levels, modulate the vasodilatory response of dural vessels, triggering and perpetuating migraine attacks. DC: Dendritic cell; 5-HT: 5-hydroxytryptamine; IL: Interleukin; CGRP: Calcitonin gene-related peptide; TG: Trigeminal ganglion; *H. pylori*: *Helicobacter pylori*.

nervous system (Figure 1).

The serotonergic system has been shown to be differentially affected by the gut microbiota in experimental studies. Whole-brain tryptophan, tyrosine and glutamine levels are lower in germ-free mice compared to those re-colonized by normal microbiota^[96], while concentrations of 5-HT and 5-hydroxyindoleacetic acid in hippocampal slices are elevated in germ-free mice^[97]. Furthermore, circulating levels of 5-HT and tyrosine are elevated in germ-free animals, compared to those with normal gut microbiota^[97,98].

CGRP functions not only as a transmitter but also as a gut hormone, and its signaling could be influenced by microbiota through multiple pathways^[99]. Although studies demonstrate changes in the expression of sensory-related peptides in the gut by modulating the whole microbiome, no direct effect has been found for CGRP^[100]. However, at least one study did show that after treatment with the probiotic *Pediococcus acidilactici*, the number of CGRP-immunoreactive neurons increased in the submucosal plexus ganglia of the small intestine^[101], although no such effect was observed with *Saccharomyces boulardii*^[102].

Whether the gut microbiome has any effects on large-scale cortical function is a matter of theoretical

debate. In an interesting study, a group of healthy volunteers who were given fermented milk product with probiotics (*Bifidobacterium animalis* subsp *Lactis*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, and *Lactococcus lactis* subsp *Lactis*) showed a reduced task-related response of a distributed functional network in affective and viscerosensory cortices on functional MRI^[103]. The results of a small, non-randomized trial, including 29 migraine patients, showed a significant reduction in migraine severity after 12 wk of probiotic supplementation compared to baseline^[104]. Moreover, an open-label study using a combination of two nutritional formulations (combination A: Enzymatically rendered fish protein high in bioactive peptides and amino acids plus probiotics and chlorophyll; combination B: Composed of 21 different ingredients designed to improve the nutritional status of the kidneys and liver) demonstrated a significant and sustained improvement in quality of life (determined by the Migraine Specific Quality of Life Questionnaire), supporting the idea that dysbiosis and altered assimilation of nutrients could have an important role in the physiopathology of migraine^[105].

There is no direct evidence to conclusively support that the gut microbiome can affect migraine. However,

Table 2 Future areas of interest on gastrointestinal disorders associated with migraine

Unanswered questions and future directions
<i>H. pylori</i>
Ethnicity difference between <i>H. pylori</i> and migraine association
Effects of different eradication therapy schemes in migraine
Impact of routine screening for <i>H. pylori</i> infection in PWM
Intrinsic role for antibiotic or antacid treatment used for <i>H. pylori</i> eradication in migraine
Effect of triptans (5-HT _{1B} and 5-HT _{1D} receptor agonist) in PWM depending their <i>H. pylori</i> infection status
Irritable bowel syndrome
Role of gluten-, wheat- and FODMAP-free diets in migraine
Effect of "dysbiosis" over serum level of cytokines and neurotransmitters in migraine
Gastroparesis
Nature, causes and consequences of gastroparesis in migraine
Determination of gastroparesis occurrence during the ictally and interictally periods in migraine
Hepato-biliary disorders
Prevalence of hepato-biliary disorders in different populations
Role of CCKB (CCK-2) receptor antagonists in migraine
Role of CCKA (CCK-1) receptors agonist in the treatment of obesity and migraine
Effect of coffee consumption in migraine in patients with NAFLD
Celiac disease
Routine screening for migraine in patients with CD
Role of interferon-gamma and TNF-alpha in the apparition/progression of migraine in patients with CD
Microbiome
Effects of normal microbiota and dysbiosis in CRGP regulation and expression
Effects of normal microbiota and dysbiosis in the serotonergic system and migraine
Role of fecal microbiota transplantation in migraine
Other GI disorders
Reflux symptoms in patients with migraine as cause of the disease itself or a side effect of antimigraine medications

PWM: Patients with migraine; CCK: Cholecystokinin; NAFLD: Non-alcoholic fatty liver disease; CD: Celiac disease; TNF: Tumor necrosis factor; CGRP: Calcitonin gene-related peptide; GI: Gastrointestinal; *H. pylori*: *Helicobacter pylori*.

the prospects of a therapeutic strategy based on probiotic dietary interventions or modifications of the gut microbiome, considering that these would intuitively have a high safety profile and cost-effectiveness, make this issue an interesting topic for further research.

FUTURE AREAS OF RESEARCH

Several unanswered questions arise related to this topic. Therefore, further research in GI disorder associated to migraine is warranted in order to evaluate the real impact of some screening and therapeutic measures as well as to clearly define the common inflammatory and neurotransmitter pathways in GI disorders and migraine (Table 2).

CONCLUSION

Currently, sufficient evidence exists linking the increased frequency of several GI disorders with migraine compared to the general population. The gut-brain axis plays an important role in the association between GI disorders and migraine. Multiple inflammatory and vasoactive mediators are significantly implicated in the physiopathology of migraine, mainly through the GI microbiota modulation of the GI immunological and autonomic system.

Based on the several implicated mechanisms between different GI disorders and migraine, several pharmacologic and non-pharmacologic therapeutic

options for specific GI disorders have shown to improve frequency and severity of migraine attacks. Also, based on the implicated mechanisms, some screening measures (*e.g.*, *H. pylori* infection) seem to be justified in PWM. Treatment of GI comorbidities in migraine might not only lead to a better quality of life but could also open roads for novel therapeutic strategies for this prevalent and disabling disease.

ACKNOWLEDGMENTS

We thank Sergio Lozano-Rodríguez, MD, for his help in editing the manuscript.

REFERENCES

- 1 **Headache Classification Committee of the International Headache Society (IHS)**. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; **33**: 629-808 [PMID: 23771276 DOI: 10.1177/0333102413485658]
- 2 **Lipton RB**, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; **68**: 343-349 [PMID: 17261680 DOI: 10.1212/01.wnl.0000252808.97649.21]
- 3 **Victor TW**, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: a life-span study. *Cephalalgia* 2010; **30**: 1065-1072 [PMID: 20713557 DOI: 10.1177/0333102409355601]
- 4 **Stovner Lj**, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, Steiner T, Zwart JA. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007; **27**: 193-210 [PMID: 17381554 DOI: 10.1111/

- j.1468-2982.2007.01288.x]
- 5 **Valade D.** Chronic migraine. *Rev Neurol (Paris)* 2013; **169**: 419-426 [PMID: 23602118 DOI: 10.1016/j.neurol.2013.01.629]
 - 6 **Natoli JL,** Manack A, Dean B, Butler Q, Turkel CC, Stovner L, Lipton RB. Global prevalence of chronic migraine: a systematic review. *Cephalalgia* 2010; **30**: 599-609 [PMID: 19614702 DOI: 10.1111/j.1468-2982.2009.01941.x]
 - 7 **Ferrari MD,** Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AM. Migraine pathophysiology: lessons from mouse models and human genetics. *Lancet Neurol* 2015; **14**: 65-80 [PMID: 25496898 DOI: 10.1016/s1474-4422(14)70220-0]
 - 8 **Nosedá R,** Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. *Pain* 2013; **154** Suppl 1: S44-S53 [PMID: 23891892 DOI: 10.1016/j.pain.2013.07.021]
 - 9 **Burstein R,** Nosedá R, Borsook D. Migraine: multiple processes, complex pathophysiology. *J Neurosci* 2015; **35**: 6619-6629 [PMID: 25926442 DOI: 10.1523/jneurosci.0373-15.2015]
 - 10 **Aamodt AH,** Stovner LJ, Hagen K, Zwart JA. Comorbidity of headache and gastrointestinal complaints. The Head-HUNT Study. *Cephalalgia* 2008; **28**: 144-151 [PMID: 18197884 DOI: 10.1111/j.1468-2982.2007.01486.x]
 - 11 **Alvarez-Arellano L,** Maldonado-Bernal C. Helicobacter pylori and neurological diseases: Married by the laws of inflammation. *World J Gastrointest Pathophysiol* 2014; **5**: 400-404 [PMID: 25400983 DOI: 10.4291/wjgp.v5.i4.400]
 - 12 **Gasbarrini A,** Franceschi F, Armuzzi A, Ojetti V, Candelli M, Torre ES, De Lorenzo A, Anti M, Pretolani S, Gasbarrini G. Extradigestive manifestations of Helicobacter pylori gastric infection. *Gut* 1999; **45** Suppl 1: I9-I12 [PMID: 10457029 DOI: 10.1136/gut.45.2008.19]
 - 13 **Mavromichalis I,** Zaramboukas T, Giala MM. Migraine of gastrointestinal origin. *Eur J Pediatr* 1995; **154**: 406-410 [PMID: 7641777 DOI: 10.1007/BF02072116]
 - 14 **Gasbarrini A,** De Luca A, Fiore G, Franceschi F, Ojetti VV, Torre ES, Di Campli C, Candelli M, Pola R, Serricchio M, Tondi P, Gasbarrini G, Pola P, Giacobovazzo M. Primary Headache and Helicobacter Pylori. *Int J Angiol* 1998; **7**: 310-312 [PMID: 9716793 DOI: 10.1007/s005479900121]
 - 15 **Gasbarrini A,** De Luca A, Fiore G, Gambrielli M, Franceschi F, Ojetti V, Torre ES, Gasbarrini G, Pola P, Giacobovazzo M. Beneficial effects of Helicobacter pylori eradication on migraine. *Hepatogastroenterology* 1998; **45**: 765-770 [PMID: 9684130]
 - 16 **Pinessi L,** Savi L, Pellicano R, Rainero I, Valfrè W, Gentile S, Cossotto D, Rizzetto M, Ponzetto A. Chronic Helicobacter pylori infection and migraine: a case-control study. *Headache* 2000; **40**: 836-839 [PMID: 11135029 DOI: 10.1046/j.1526-4610.2000.00151.x]
 - 17 **Gasbarrini A,** Gabrielli M, Fiore G, Candelli M, Bartolozzi F, De Luca A, Cremonini F, Franceschi F, Di Campli C, Armuzzi A, Ojetti V, Serricchio M, Pola R, Gasbarrini G, Giacobovazzo M, Pola P. Association between Helicobacter pylori cytotoxic type I CagA-positive strains and migraine with aura. *Cephalalgia* 2000; **20**: 561-565 [PMID: 11075839 DOI: 10.1046/j.1468-2982.2000.00077.x]
 - 18 **Tunca A,** Türkay C, Tekin O, Kargili A, Erbayrak M. Is Helicobacter pylori infection a risk factor for migraine? A case-control study. *Acta Neurol Belg* 2004; **104**: 161-164 [PMID: 15742606]
 - 19 **Yiannopoulou KG,** Efthymiou A, Karydakis K, Arhimandritis A, Bovaretos N, Tzivras M. Helicobacter pylori infection as an environmental risk factor for migraine without aura. *J Headache Pain* 2007; **8**: 329-333 [PMID: 18071631 DOI: 10.1007/s10194-007-0422-7]
 - 20 **Su J,** Zhou XY, Zhang GX. Association between Helicobacter pylori infection and migraine: a meta-analysis. *World J Gastroenterol* 2014; **20**: 14965-14972 [PMID: 25356058 DOI: 10.3748/wjg.v20.i40.14965]
 - 21 **Ansari B,** Basiri K, Omeamar R, Chitsaz A, Nematollahi S. Association of Helicobacter pylori antibodies and severity of migraine attack. *Iran J Neurol* 2015; **14**: 125-129 [PMID: 26622976]
 - 22 **Faraji F,** Zarinfar N, Zanjani AT, Morteza A. The effect of Helicobacter pylori eradication on migraine: a randomized, double blind, controlled trial. *Pain Physician* 2012; **15**: 495-498 [PMID: 23159967]
 - 23 **Ciancarelli I,** Di Massimo C, Tozzi-Ciancarelli MG, De Matteis G, Marini C, Carolei A. Helicobacter pylori infection and migraine. *Cephalalgia* 2002; **22**: 222-225 [PMID: 12047462 DOI: 10.1046/j.1468-2982.2002.00354.x]
 - 24 **Tunca A,** Ardiçoğlu Y, Kargili A, Adam B. Migraine, Helicobacter pylori, and oxidative stress. *Helicobacter* 2007; **12**: 59-62 [PMID: 17241302 DOI: 10.1111/j.1523-5378.2007.00470.x]
 - 25 **Kang JW,** Shin YI. The role of interleukin 10 in the associations between migraine and Helicobacter pylori infection. *Pain Physician* 2013; **16**: E450 [PMID: 23877472]
 - 26 **Munno I,** Marinaro M, Bassi A, Cassiano MA, Causarano V, Centonze V. Immunological aspects in migraine: increase of IL-10 plasma levels during attack. *Headache* 2001; **41**: 764-767 [PMID: 11576199 DOI: 10.1046/j.1526-4610.2001.01140.x]
 - 27 **Cernuda-Morollón E,** Larrosa D, Ramón C, Vega J, Martínez-Cambor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. *Neurology* 2013; **81**: 1191-1196 [PMID: 23975872 DOI: 10.1212/WNL.0b013e3182a6cb72]
 - 28 **Yang H,** Zou Y, Zhang X. [Determination of serum calicotonin gene-related peptide in patients with duodenal ulcer infected with Helicobacter pylori]. *Hunan Yike Daxue Xuebao* 1999; **24**: 273-274 [PMID: 12016804]
 - 29 **Savi L,** Ribaldone DG, Fagoonee S, Pellicano R. Is Helicobacter pylori the infectious trigger for headache?: A review. *Infect Disord Drug Targets* 2013; **13**: 313-317 [PMID: 24304354 DOI: 10.2174/1871526513666131201125021]
 - 30 **Chang FY,** Lu CL. Irritable bowel syndrome and migraine: bystanders or partners? *J Neurogastroenterol Motil* 2013; **19**: 301-311 [PMID: 23875096 DOI: 10.5056/jnm.2013.19.3.301]
 - 31 **Riedl A,** Schmidtman M, Stengel A, Goebel M, Wisser AS, Klapp BF, Mönnikes H. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res* 2008; **64**: 573-582 [PMID: 18501257 DOI: 10.1016/j.jpsychores.2008.02.021]
 - 32 **Whitehead WE,** Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology* 2002; **122**: 1140-1156 [PMID: 11910364 DOI: 10.1053/gast.2002.32392]
 - 33 **Jones R,** Lydeard S. Irritable bowel syndrome in the general population. *BMJ* 1992; **304**: 87-90 [PMID: 1737146 DOI: 10.1136/bmj.304.6819.87]
 - 34 **Tietjen GE,** Herial NA, Hardgrove J, Utley C, White L. Migraine comorbidity constellations. *Headache* 2007; **47**: 857-865 [PMID: 17578536 DOI: 10.1111/j.1526-4610.2007.00814.x]
 - 35 **Vandvik PO,** Wilhelmsen I, Ihlebaek C, Farup PG. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. *Aliment Pharmacol Ther* 2004; **20**: 1195-1203 [PMID: 15569123 DOI: 10.1111/j.1365-2036.2004.02250.x]
 - 36 **Cole JA,** Rothman KJ, Cabral HJ, Zhang Y, Farraye FA. Migraine, fibromyalgia, and depression among people with IBS: a prevalence study. *BMC Gastroenterol* 2006; **6**: 26 [PMID: 17007634 DOI: 10.1186/1471-230x-6-26]
 - 37 **Lau CI,** Lin CC, Chen WH, Wang HC, Kao CH. Association between migraine and irritable bowel syndrome: a population-based retrospective cohort study. *Eur J Neurol* 2014; **21**: 1198-1204 [PMID: 24838228 DOI: 10.1111/ene.12468]
 - 38 **Guthrie EA,** Creed FH, Whorwell PJ, Tomenson B. Outpatients with irritable bowel syndrome: a comparison of first time and chronic attenders. *Gut* 1992; **33**: 361-363 [PMID: 1568655 DOI: 10.1136/gut.33.3.361]
 - 39 **Park JW,** Cho YS, Lee SY, Kim ES, Cho H, Shin HE, Suh GI, Choi MG. Concomitant functional gastrointestinal symptoms influence psychological status in Korean migraine patients. *Gut Liver* 2013; **7**: 668-674 [PMID: 24312707 DOI: 10.5009/gnl.2013.7.6.668]
 - 40 **Aydinlar EI,** Dikmen PY, Tiftkci A, Saruc M, Aksu M, Gunsoy HG, Tozun N. IgG-based elimination diet in migraine plus irritable bowel syndrome. *Headache* 2013; **53**: 514-525 [PMID: 23216231]

- DOI: 10.1111/j.1526-4610.2012.02296.x]
- 41 **Aurora SK**, Papapetropoulos S, Kori SH, Kedar A, Abell TL. Gastric stasis in migraineurs: etiology, characteristics, and clinical and therapeutic implications. *Cephalalgia* 2013; **33**: 408-415 [PMID: 23463252 DOI: 10.1177/0333102412473371]
 - 42 **Carstairs LS**. Headache and gastric emptying time. *Proc R Soc Med* 1958; **51**: 790-791; discussion 791-793 [PMID: 13601720]
 - 43 **Volans GN**. Migraine and drug absorption. *Clin Pharmacokinet* 1978; **3**: 313-318 [PMID: 354637 DOI: 10.2165/00003088-197803040-00004]
 - 44 **Tokola RA**, Neuvonen PJ. Effect of migraine attacks on paracetamol absorption. *Br J Clin Pharmacol* 1984; **18**: 867-871 [PMID: 6529526 DOI: 10.1111/j.1365-2125.1984.tb02557.x]
 - 45 **Boyle R**, Behan PO, Sutton JA. A correlation between severity of migraine and delayed gastric emptying measured by an epigastric impedance method. *Br J Clin Pharmacol* 1990; **30**: 405-409 [PMID: 2223419 DOI: 10.1111/j.1365-2125.1990.tb03791.x]
 - 46 **De Ponti F**. Pharmacology of emesis and gastrointestinal motility: implications for migraine. *Funct Neurol* 2000; **15** Suppl 3: 43-49 [PMID: 11200800]
 - 47 **Aurora SK**, Kori SH, Barrodale P, McDonald SA, Haseley D. Gastric stasis in migraine: more than just a paroxysmal abnormality during a migraine attack. *Headache* 2006; **46**: 57-63 [PMID: 16412152 DOI: 10.1111/j.1526-4610.2006.00311.x]
 - 48 **Pucci E**, Di Stefano M, Miceli E, Corazza GR, Sandrini G, Nappi G. Patients with headache and functional dyspepsia present meal-induced hypersensitivity of the stomach. *J Headache Pain* 2005; **6**: 223-226 [PMID: 16362670 DOI: 10.1007/s10194-005-0191-0]
 - 49 **Aurora S**, Kori S, Barrodale P, Nelsen A, McDonald S. Gastric stasis occurs in spontaneous, visually induced, and interictal migraine. *Headache* 2007; **47**: 1443-1446 [PMID: 17868348 DOI: 10.1111/j.1526-4610.2007.00922.x]
 - 50 **Yalcin H**, Okuyucu EE, Ucar E, Duman T, Yilmazer S. Changes in liquid emptying in migraine patients: diagnosed with liquid phase gastric emptying scintigraphy. *Intern Med J* 2012; **42**: 455-459 [PMID: 22498119 DOI: 10.1111/j.1445-5994.2012.02741.x]
 - 51 **Yu YH**, Jo Y, Jung JY, Kim BK, Seok JW. Gastric emptying in migraine: a comparison with functional dyspepsia. *J Neurogastroenterol Motil* 2012; **18**: 412-418 [PMID: 23106002 DOI: 10.5056/jnm.2012.18.4.412]
 - 52 **Lee KJ**. Gastric emptying in patients with functional dyspepsia and patients with migraine. *J Neurogastroenterol Motil* 2013; **19**: 116-117 [PMID: 23350061 DOI: 10.5056/jnm.2013.19.1.116]
 - 53 **Parkman HP**. Migraine and gastroparesis from a gastroenterologist's perspective. *Headache* 2013; **53** Suppl 1: 4-10 [PMID: 23721284 DOI: 10.1111/head.12112]
 - 54 **Krymchantowski AV**, Filho PF, Bigal ME. Rizatriptan vs. rizatriptan plus trimebutine for the acute treatment of migraine: a double-blind, randomized, cross-over, placebo-controlled study. *Cephalalgia* 2006; **26**: 871-874 [PMID: 16776704 DOI: 10.1111/j.1468-2982.2006.01136.x]
 - 55 **Inaloo S**, Dehghani SM, Hashemi SM, Heydari M, Heydari ST. Comorbidity of headache and functional constipation in children: a cross-sectional survey. *Turk J Gastroenterol* 2014; **25**: 508-511 [PMID: 25417610 DOI: 10.5152/tjg.2014.6183]
 - 56 **Park MN**, Choi MG, You SJ. The relationship between primary headache and constipation in children and adolescents. *Korean J Pediatr* 2015; **58**: 60-63 [PMID: 25774197 DOI: 10.3345/kjp.2015.58.2.60]
 - 57 **Katić BJ**, Golden W, Cady RK, Hu XH. GERD prevalence in migraine patients and the implication for acute migraine treatment. *J Headache Pain* 2009; **10**: 35-43 [PMID: 19009231 DOI: 10.1007/s10194-008-0083-1]
 - 58 **Abramson JH**, Gofin J, Peritz E, Hopp C, Epstein LM. Clustering of chronic disorders--a community study of coprevalence in Jerusalem. *J Chronic Dis* 1982; **35**: 221-230 [PMID: 7061679 DOI: 10.1016/0021-9681(82)90143-6]
 - 59 **Kurth T**, Holtmann G, Neufang-Hüber J, Gerken G, Diener HC. Prevalence of unexplained upper abdominal symptoms in patients with migraine. *Cephalalgia* 2006; **26**: 506-510 [PMID: 16674758 DOI: 10.1111/j.1468-2982.2005.01076.x]
 - 60 **Nilsson S**, Edvinsson L, Malmberg B, Johansson B, Linde M. A relationship between migraine and biliary tract disorders: findings in two Swedish samples of elderly twins. *Acta Neurol Scand* 2010; **122**: 286-294 [PMID: 20047569 DOI: 10.1111/j.1600-0404.2009.01310.x]
 - 61 **Aggarwal N**, Bielefeldt K. Diagnostic stringency and healthcare needs in patients with biliary dyskinesia. *Dig Dis Sci* 2013; **58**: 2799-2808 [PMID: 23934412 DOI: 10.1007/s10620-013-2719-5]
 - 62 **Steiner TJ**, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. *J Headache Pain* 2013; **14**: 1 [PMID: 23566305 DOI: 10.1186/1129-2377-14-1]
 - 63 **O'Connor TP**, van der Kooy D. Enrichment of a vasoactive neuropeptide (calcitonin gene related peptide) in the trigeminal sensory projection to the intracranial arteries. *J Neurosci* 1988; **8**: 2468-2476 [PMID: 2470872]
 - 64 **Kline LW**, Pang PK. The effect of body weight on the calcitonin gene-related peptide-induced relaxation of guinea pig gallbladder strips. *Regul Pept* 1995; **59**: 97-101 [PMID: 12506419 DOI: 10.1016/0167-0115(95)00078-P]
 - 65 **Mulvihill SJ**, Yan P. Impaired release of gallbladder calcitonin gene-related peptide in human gallstone disease. *J Surg Res* 1995; **58**: 641-645 [PMID: 7791341 DOI: 10.1006/jsre.1995.1101]
 - 66 **Ruiz-Gayo M**, González MC, Fernández-Alfonso S. Vasodilatory effects of cholecystokinin: new role for an old peptide? *Regul Pept* 2006; **137**: 179-184 [PMID: 16889840 DOI: 10.1016/j.regpep.2006.06.006]
 - 67 **Rodríguez RR**, Saccone J, Véliz MA. Headache and liver disease: is their relationship more apparent than real? *Dig Dis Sci* 2004; **49**: 1016-1018 [PMID: 15309894 DOI: 10.1023/B:DDAS.0000034565.40011.60]
 - 68 **Celikbilek A**, Celikbilek M, Okur A, Dogan S, Borekci E, Kozan M, GURSOY S. Non-alcoholic fatty liver disease in patients with migraine. *Neurol Sci* 2014; **35**: 1573-1578 [PMID: 24756192 DOI: 10.1007/s10072-014-1798-1]
 - 69 **Ornello R**, Ripa P, Pistoia F, Degan D, Tiseo C, Carolei A, Sacco S. Migraine and body mass index categories: a systematic review and meta-analysis of observational studies. *J Headache Pain* 2015; **16**: 27 [PMID: 25903159 DOI: 10.1186/s10194-015-0510-z]
 - 70 **Verrotti A**, Carotenuto M, Altieri L, Parisi P, Tozzi E, Belcastro V, Esposito M, Guastaferrro N, Ciuti A, Mohn A, Chiarelli F, Agostinelli S. Migraine and obesity: metabolic parameters and response to a weight loss programme. *Pediatr Obes* 2015; **10**: 220-225 [PMID: 24990114 DOI: 10.1111/ijpo.245]
 - 71 **Pilichiewicz AN**, Little TJ, Brennan IM, Meyer JH, Wishart JM, Otto B, Horowitz M, Feinle-Bisset C. Effects of load, and duration, of duodenal lipid on antropyloroduodenal motility, plasma CCK and PYY, and energy intake in healthy men. *Am J Physiol Regul Integr Comp Physiol* 2006; **290**: R668-R677 [PMID: 16210415 DOI: 10.1152/ajpregu.00606.2005]
 - 72 **Matzinger D**, Degen L, Drewe J, Meuli J, Duebendorfer R, Ruckstuhl N, D'Amato M, Rovati L, Beglinger C. The role of long chain fatty acids in regulating food intake and cholecystokinin release in humans. *Gut* 2000; **46**: 688-693 [PMID: 10764713 DOI: 10.1136/gut.46.5.689]
 - 73 **Ferrara LA**, Pacioni D, Di Fronzo V, Russo BF, Speranza E, Carlino V, Gargiulo F, Ferrara F. Low-lipid diet reduces frequency and severity of acute migraine attacks. *Nutr Metab Cardiovasc Dis* 2015; **25**: 370-375 [PMID: 25698152 DOI: 10.1016/j.numecd.2014.12.006]
 - 74 **Green PH**, Cellier C. Celiac disease. *N Engl J Med* 2007; **357**: 1731-1743 [PMID: 17960014 DOI: 10.1056/NEJMra071600]
 - 75 **Bushara KO**. Neurologic presentation of celiac disease. *Gastroenterology* 2005; **128**: S92-S97 [PMID: 15825133 DOI: 10.1053/j.gastro.2005.02.018]
 - 76 **Serratrice J**, Disdier P, de Roux C, Christides C, Weiller PJ. Migraine and coeliac disease. *Headache* 1998; **38**: 627-628 [PMID: 11398309 DOI: 10.1046/j.1526-4610.1998.3808627.x]
 - 77 **D'Amico D**, Rigamonti A, Spina L, Bianchi-Marzoli S, Vecchi M, Bussone G. Migraine, celiac disease, and cerebral calcifications: a

- new case. *Headache* 2005; **45**: 1263-1267 [PMID: 16178961 DOI: 10.1111/j.1526-4610.2005.00253_2.x]
- 78 **Benjilali L**, Zahlane M, Essaadouni L. A migraine as initial presentation of celiac disease. *Rev Neurol (Paris)* 2012; **168**: 454-456 [PMID: 22405455 DOI: 10.1016/j.neurol.2011.10.008]
- 79 **Lahat E**, Broide E, Leshem M, Evans S, Scapa E. Prevalence of celiac antibodies in children with neurologic disorders. *Pediatr Neurol* 2000; **22**: 393-396 [PMID: 10913732 DOI: 10.1016/S0887-8994(00)00129-6]
- 80 **Schlesinger I**, Hering R. Antigliadin antibodies in migraine patients. *Cephalalgia* 1997; **17**: 712 [PMID: 9350395 DOI: 10.1177/033310249701700616]
- 81 **Armstrong D**, Don-Wauchope AC, Verdu EF. Testing for gluten-related disorders in clinical practice: the role of serology in managing the spectrum of gluten sensitivity. *Can J Gastroenterol* 2011; **25**: 193-197 [PMID: 21523259 DOI: 10.1155/2011/642452]
- 82 **Inaloo S**, Dehghani SM, Farzadi F, Haghghat M, Imanieh MH. A comparative study of celiac disease in children with migraine headache and a normal control group. *Turk J Gastroenterol* 2011; **22**: 32-35 [PMID: 21480108 DOI: 10.4318/tjg.2011.0153]
- 83 **Alehan F**, Özçay F, Erol I, Canan O, Cemil T. Increased risk for coeliac disease in paediatric patients with migraine. *Cephalalgia* 2008; **28**: 945-949 [PMID: 18624809 DOI: 10.1111/j.1468-2982.2008.01630.x]
- 84 **Bürk K**, Farecki ML, Lamprecht G, Roth G, Decker P, Weller M, Rammensee HG, Oertel W. Neurological symptoms in patients with biopsy proven celiac disease. *Mov Disord* 2009; **24**: 2358-2362 [PMID: 19845007 DOI: 10.1002/mds.22821]
- 85 **Dimitrova AK**, Ungaro RC, Lebwohl B, Lewis SK, Tennyson CA, Green MW, Babyatsky MW, Green PH. Prevalence of migraine in patients with celiac disease and inflammatory bowel disease. *Headache* 2013; **53**: 344-355 [PMID: 23126519 DOI: 10.1111/j.1526-4610.2012.02260.x]
- 86 **Lionetti E**, Francavilla R, Maiuri L, Ruggieri M, Spina M, Pavone P, Francavilla T, Magistà AM, Pavone L. Headache in pediatric patients with celiac disease and its prevalence as a diagnostic clue. *J Pediatr Gastroenterol Nutr* 2009; **49**: 202-207 [PMID: 19543115 DOI: 10.1097/MPG.0b013e31818f6389]
- 87 **Gabrielli M**, Cremonini F, Fiore G, Addolorato G, Padalino C, Candelli M, De Leo ME, Santarelli L, Giacobozzo M, Gasbarrini A, Pola P, Gasbarrini A. Association between migraine and Celiac disease: results from a preliminary case-control and therapeutic study. *Am J Gastroenterol* 2003; **98**: 625-629 [PMID: 12650798 DOI: 10.1111/j.1572-0241.2003.07300.x]
- 88 **Cicarelli G**, Della Rocca G, Amboni M, Ciacci C, Mazzacca G, Filla A, Barone P. Clinical and neurological abnormalities in adult celiac disease. *Neurol Sci* 2003; **24**: 311-317 [PMID: 14716525 DOI: 10.1007/s10072-003-0181-4]
- 89 **Zelnik N**, Pacht A, Obeid R, Lerner A. Range of neurologic disorders in patients with celiac disease. *Pediatrics* 2004; **113**: 1672-1676 [PMID: 15173490 DOI: 10.1542/peds.113.6.1672]
- 90 **Hadjivassiliou M**, Grünewald RA, Lawden M, Davies-Jones GA, Powell T, Smith CM. Headache and CNS white matter abnormalities associated with gluten sensitivity. *Neurology* 2001; **56**: 385-388 [PMID: 11171906 DOI: 10.1212/WNL.56.3.385]
- 91 **Cady RK**, Farmer K, Dexter JK, Hall J. The bowel and migraine: update on celiac disease and irritable bowel syndrome. *Curr Pain Headache Rep* 2012; **16**: 278-286 [PMID: 22447132 DOI: 10.1007/s11916-012-0258-y]
- 92 **Briani C**, Zara G, Alaedini A, Grassivaro F, Ruggero S, Toffanin E, Albergoni MP, Luca M, Giometto B, Ermani M, De Lazzari F, D'Odorico A, Battistin L. Neurological complications of celiac disease and autoimmune mechanisms: a prospective study. *J Neuroimmunol* 2008; **195**: 171-175 [PMID: 18343508 DOI: 10.1016/j.jneuroim.2008.01.008]
- 93 **Mormile R**. Celiac disease and migraine: is there a common backstage? *Int J Colorectal Dis* 2014; **29**: 1571 [PMID: 24965856 DOI: 10.1007/s00384-014-1923-x]
- 94 **Mayer EA**, Tillisch K, Gupta A. Gut/brain axis and the microbiota. *J Clin Invest* 2015; **125**: 926-938 [PMID: 25689247 DOI: 10.1172/jci76304]
- 95 **Hindiyeh N**, Aurora SK. What the Gut Can Teach Us About Migraine. *Curr Pain Headache Rep* 2015; **19**: 33 [PMID: 26049770 DOI: 10.1007/s11916-015-0501-4]
- 96 **Matsumoto M**, Kibe R, Ooga T, Aiba Y, Sawaki E, Koga Y, Benno Y. Cerebral low-molecular metabolites influenced by intestinal microbiota: a pilot study. *Front Syst Neurosci* 2013; **7**: 9 [PMID: 23630473 DOI: 10.3389/fnsys.2013.00009]
- 97 **Clarke G**, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, Dinan TG, Cryan JF. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol Psychiatry* 2013; **18**: 666-673 [PMID: 22688187 DOI: 10.1038/mp.2012.77]
- 98 **Wikoff WR**, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, Siuzdak G. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc Natl Acad Sci USA* 2009; **106**: 3698-3703 [PMID: 19234110 DOI: 10.1073/pnas.0812874106]
- 99 **Holzer P**, Farzi A. Neuropeptides and the microbiota-gut-brain axis. *Adv Exp Med Biol* 2014; **817**: 195-219 [PMID: 24997035 DOI: 10.1007/978-1-4939-0897-4_9]
- 100 **Aguilera M**, Vergara P, Martínez V. Environment-related adaptive changes of gut commensal microbiota do not alter colonic toll-like receptors but modulate the local expression of sensory-related systems in rats. *Microb Ecol* 2013; **66**: 232-243 [PMID: 23666270 DOI: 10.1007/s00248-013-0241-0]
- 101 **di Giancamillo A**, Vitari F, Bosi G, Savoini G, Domeneghini C. The chemical code of porcine enteric neurons and the number of enteric glial cells are altered by dietary probiotics. *Neurogastroenterol Motil* 2010; **22**: e271-e278 [PMID: 20524986 DOI: 10.1111/j.1365-2982.2010.01529.x]
- 102 **Kamm K**, Hoppe S, Breves G, Schröder B, Schemann M. Effects of the probiotic yeast *Saccharomyces boulardii* on the neurochemistry of myenteric neurones in pig jejunum. *Neurogastroenterol Motil* 2004; **16**: 53-60 [PMID: 14764205 DOI: 10.1046/j.1365-2982.2003.00458.x]
- 103 **Tillisch K**, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain-Raspaud S, Trotin B, Naliboff B, Mayer EA. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* 2013; **144**: 1394-1401, 1401.e1-4 [PMID: 23474283 DOI: 10.1053/j.gastro.2013.02.043]
- 104 **de Roos NM**, Giezenaar CG, Rovers JM, Witteman BJ, Smits MG, van Hemert S. The effects of the multispecies probiotic mixture Ecologic@Barrier on migraine: results of an open-label pilot study. *Benef Microbes* 2015; **6**: 641-646 [PMID: 25869282 DOI: 10.3920/bm2015.0003]
- 105 **Sensenig J**, Johnson M, Staverosky T. Treatment of migraine with targeted nutrition focused on improved assimilation and elimination. *Altern Med Rev* 2001; **6**: 488-494 [PMID: 11703169]

P- Reviewer: Auricchio S, Doherty GA, Garcia-Olmo D, Gonzalez-Reimers E, Paydas S

S- Editor: Qi Y **L- Editor:** Filipodia **E- Editor:** Zhang FF





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327

