

REVIEW ARTICLE

Gastrointestinal Headache; a Narrative Review

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Abstract

There are studies reporting primary headaches to be associated with gastrointestinal disorders, and some report resolution of headache following the treatment of the associated gastrointestinal disorder. Headache disorders are classified by The International Headache Society as primary or secondary; however, among the secondary headaches, those attributed to gastrointestinal disorders are not appreciated. Therefore, we aimed to review the literature to provide evidence for headaches, which originate from the gastrointestinal system. Gastrointestinal disorders that are reported to be associated with primary headaches include dyspepsia, gastro esophageal reflux disease (GERD), constipation, functional abdominal pain, inflammatory bowel syndrome (IBS), inflammatory bowel disorders (IBD), celiac disease, and helicobacter pylori (*H. Pylori*) infection. Some studies have demonstrated remission or improvement of headache following the treatment of the accompanying gastrointestinal disorders. Hypotheses explaining this association are considered to be central sensitization and parasympathetic referred pain, serotonin pathways, autonomic nervous system dysfunction, systemic vasculopathy, and food allergy. Traditional Persian physicians, namely Ebn-e-Sina (Avicenna) and Râzi (Rhazes) believed in a type of headache originating from disorders of the stomach and named it as an individual entity, the "Participatory Headache of Gastric Origin". We suggest providing a unique diagnostic entity for headaches coexisting with any gastrointestinal abnormality that are improved or cured along with the treatment of the gastrointestinal disorder.

Keywords: Headache; migraine disorders; gastrointestinal diseases; medicine, traditional; headache disorders, primary; headache disorders, secondary

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Introduction:

Headache is one of the common reasons for daily visits to emergency departments (ED). Sadly, in some cases despite all the diagnostic and treatment measures, the cause of the headache cannot be determined and only symptoms are treated. In these cases, the patient experiences decreased quality of life and relapse, and therefore frequently revisits ED and neurologic clinics. The international headache society (IHS) released the second edition of the international classification of headache disorders (the ICHD-II) in 2004, and the ICHD-III (beta version) recently, with which various headache disorders are diagnosed by physicians throughout the globe. Primary headaches, which are not considered to be attributed to another disorder are partly found to be cured or relieved by management of

gastrointestinal (GI) abnormalities in the affected patients (1, 2). In the initial evaluations, some probable causes of headaches, such as GI disorders, are overlooked. Providing evidence for primary headaches associated with GI disorders, may help classify this type of headache as a unique diagnostic entity. Ancient Persian physicians believed in a type of headache arising from disorders of the stomach and as an individual entity, described it in their writings as *participatory headache of gastric origin* or simply, "Gastric Headache" (3). We therefore, performed a review of the available literature to show the extent of the studies demonstrating the prevalence of headache and GI disorders' coexistence, as well as studies proposing GI abnormalities as etiologies for headaches in which, treatments targeting the GI dysfunction relieved the headache.



Methods:

Review of the available literature from 1980 to July 2014, through a PubMed search was provided. Searching the MeSH terms “Gastrointestinal Diseases” or “Migraine Disorders” or “Headache Disorders” by the PubMed search builder altogether revealed roughly 900 articles. Abstracts from pertinent articles were obtained. There were no language restrictions. If the study pointed to the association of any headache disorder with GI dysfunctions the paper was completely studied. In addition, bibliography and citations to the selected studies were evaluated and relevant articles not found previously were also included in order to augment the search results. In addition, a MEDLINE search was conducted using the keywords “Iranian Traditional Medicine”, “Persian Medicine”, and “Islamic Medicine” and relevant papers were extracted. Finally, principle texts of Traditional Persian Medicine and the highly credited manuscripts on the subject of headache were studied.

Results:

- *Dyspepsia*

Dyspepsia, defined as postprandial fullness, early satiety, or epigastric pain or burning by the Rome Committee, is reported to be present in a significant number of patients suffering from migraine (Table 1). Kurth et al. studied a population of migraineurs and compared them with a group of controls using a bowel disease questionnaire and reported pain centered in the upper abdomen to be significantly more frequent among patients with migraine (4). In another case-control study conducted by Meucci et al. among dyspeptic patients, it was noted that this group of patients suffer significantly from migraine compared to the control group. It was suggested that dyspeptic patients of the dysmotility-like or with nausea / vomiting referred for endoscopy be worked up for a diagnosis of migraine. Given the completely normal endoscopic appearance seen in 90% of the migraineurs it was concluded that dyspeptic symptoms may be a consequence of the migraine (5). Mavromichalis et al. however, demonstrated underlying inflammatory lesion in 29 of the 31 migraineurs undergoing endoscopy, supporting a causal link between GI inflammation and migraine. Treatment targeting the GI tract resulted in relief of migraine (6).

Since the former two studies were not interventional, one could not conclude whether treatment of dyspepsia would have attenuated migraine headaches. However, Sung Hwang et al. demonstrated the resolution of headache in a group of children with epigastric pain or tenderness diagnosed with primary headache after initiating regular anti-acid medication (7). Spierings reported a 50 year old dyspeptic male complaining of headache since early adulthood. Patient’s dyspeptic symptoms were treated by Cisapride 20 mg daily before dinner and

subsequently the headache was almost completely resolved (2). Interventional studies are needed to provide more evidence to support the concept that in at least some migraineurs, their dyspeptic symptoms are the cause of their headaches.

- *Gastroesophageal Reflux Disease*

Gastroesophageal reflux disease (GERD), described as abnormal reflux of gastric contents into the esophagus resulting in symptoms or mucosal damage, may manifest with typical and atypical symptoms (8). However, among the extra-esophageal symptoms, headache is not pronounced as other atypical symptoms are. There is a growing body of literature demonstrating the association of headache with reflux symptoms (Table 1).

Aamodt et al. performed the Head-HUNT study involving more than 43,000 individuals and reported reflux symptoms to be the most common symptom in this population with a rough prevalence of 30%. Headache was noted to have a higher prevalence among individuals with much reflux symptoms compared to those without such complaints. In this study, patients suffering from headache were classified into migrainous and non-migrainous (9). In another study, Katic et al. aimed to determine the prevalence of GERD and heartburn in a group of more than 1800 migraine patients. Almost half of the migraineurs were reported to have GERD, heartburn, or related symptoms and this group suffered from more severe migraines and greater frequency of attacks (10).

A population based study, enrolling close to 2000 individuals, reported significant correlation between headache and symptoms associated with GERD. It was noted that some patients’ headaches intensified with increased heartburn, and therefore, headaches were assumed to be a complication of GERD. The types of headaches, however, were not classified in this study (11).

Spierings reported two patients with headaches associated with reflux, in whom proton pump inhibitors resolved their headaches (1). Further interventional studies targeting acid reflux suppression in patients affected by both disorders may be of benefit for understanding the causal relationship.

- *Constipation*

Constipation is well known as a factor precipitating encephalopathy in patients with advanced liver disease. The mechanism involves retention of waste materials in the gut and reabsorption of toxic elements namely ammonia through blood circulation, reaching the brain and causing central nervous system (CNS) dysfunction (12). However, when hepatic function is not compromised, the ammonia is cleared out of the circulation and therefore, constipation is not considered to cause any significant disturbance. On the other hand, there is evidence that constipation may be associated with headache, raising the question about the impact of constipation on CNS even in the absence of advanced liver disease.



Table 1: Gastrointestinal disorders reported to be associated with headache including migraine

| Study | Year | Country | Sample size | Age group | Gender (female) | Findings |
|----------------------------|------|---------|-------------|--------------------|-----------------|---|
| Dyspepsia | | | | | | |
| Mavromichalis et al. (13) | 1997 | Greece | 31 | Children | 58.1% | There is causal link between recurrent abdominal pain and migraine. |
| Spierings* (1) | 2002 | USA | 2 | Adult | 100% | The dyspepsia triggered headaches. |
| Meucci et al. (5) | 2005 | Italy | 698 | Adult | 39.2% | Migraine is associated with dysmotility-like dyspepsia. |
| Pucci et al. (14) | 2005 | Italy | 14 | Adult | 85.7% | There is causal link between recurrent abdominal pain and migraine. |
| Aurora et al. (15) | 2006 | Sweden | 20 | Adult | 75% | Migraines patients suffer from gastric stasis both during and outside an acute migraine attack. |
| Kurth et al. (4) | 2006 | Germany | 587 | Adult | 46.5% | Upper abdominal symptoms are significantly more frequent in patients with migraine compared with healthy controls |
| Hwang et al.* (7) | 2008 | Korea | 58 | Children | 70% | The study supports any specific correlation between headache and epigastric pain or tenderness |
| Modiri et al. (16) | 2012 | USA | 84 | Adult | 82.1% | Headaches, especially migraines, are present in two-thirds of patients with gastroparesis. |
| Reflux symptoms | | | | | | |
| Spierings* (1) | 2002 | USA | 2 | Adult | 100% | The reflux triggered headaches and responded to specific reflux treatment. |
| Aamodt et al. (9) | 2008 | Norway | 43,782 | Adult/ Children | 63.3% | The finding may suggest that headache sufferers generally are predisposed to reflux. |
| Saberi-Firoozi et al. (11) | 2007 | Iran | 1,956 | Adult | 64.8% | gastroesophageal reflux disease is associated with headache. |
| Katic et al. (10) | 2009 | USA | 1,832 | Adult | 73% | 22.0% OF migraineurs reported having diagnosed GERD and 15.8% reported reflux symptoms. |
| Constipation | | | | | | |
| Aamodt et al. (9) | 2008 | Norway | 43,782 | Adult/ Children | 63.3% | The finding showed prevalence of the migraine was higher in constipate patients. |
| Inaloo et al. (17) | 2014 | Iran | 326 | Children | 48.2% | The study showed a strong correlation between headache and chronic functional constipation |
| Park et al. (18) | 2015 | Korea | 168 | Children | 52.1% | Resolution of constipation improves headache in many patients diagnosed with primary headache |

* , Studies in which headache was reported to improve or resolve following management of the GI disorder.

Table 1: Continue...

| Study | Year | Country | Sample size | Age group | Gender (female) | Findings |
|-------------------------------------|------|------------------|-------------|-------------|-----------------|--|
| Abdominal pain | | | | | | |
| Anttila et al. (19) | 2001 | Finland | 513 | Children | 49.9% | Children with migraine and nonmigrainous headaches report higher frequencies of abdominal pain. |
| Groholt et al. (20) | 2003 | Nordic countries | 6,230 | Children | 46.7% | There was an association between the abdominal pain and incidence of headache. |
| Boccia et al. (21) | 2006 | Italy | 60 | Children | 58% | Most children with migraine report FGIDs, associated with a delayed gastric emptying |
| Walker et al. (22) | 2010 | USA | 200 | Young adult | 62% | Children with abdominal pain that persists into adulthood may be at increased risk for headache. |
| Dengler-Crish et al. (23) | 2011 | USA | 249 | Children | 67.9% | Children with functional abdominal pain may identify a group that is at risk for headache later in life. |
| Chelimsky et al. (24) | 2012 | USA | 38 | Children | 63.2% | 40% of functional gastrointestinal disorders patients had migraine. |
| Inflammatory bowel syndrome | | | | | | |
| Vandvik et al. (25) | 2004 | Norway | 208 | Adult | 67% | 44.7% of patients with irritable bowel syndrome suffer from headache or migraine. |
| Hershfield et al. (26) | 2005 | Canada | 200 | Adult | 64.5% | 47% of patients with irritable bowel syndrome Have headache. |
| Agrawal et al. (27) | 2009 | UK | 211 | Old adult | 65.2% | 50% of patients with irritable bowel syndrome suffer from headache. |
| Park et al. (28) | 2013 | Korea | 109 | Adult | 87.2 | 40.4% of migraine patients have irritable bowel syndrome. |
| Inflammatory bowel disorders | | | | | | |
| Hershfield et al. (26) | 2005 | Canada | 200 | Adult | 66.5% | 19% of patients with irritable bowel syndrome suffer from headache. |
| Oliviera et al. (29) | 2008 | Brazil | 82 | Adult | 51.2% | Neurological disorders, such as headache, are common in inflammatory bowel disease patients |
| Ford et al. (30) | 2009 | USA | 100 | Adult | 77% | The prevalence of migraine in the inflammatory bowel disease sample was 30%. Migraine was more prevalent in the CD subjects (36%) than UC subjects (14.8%) |
| Dimitrova et al. (31) | 2013 | USA | 502 | Adult | 67.3% | Migraine was more prevalent in celiac disease and inflammatory bowel disease subjects than in controls. |

* , Studies in which headache was reported to improve or resolve following management of the GI disorder.



Table 1: Continue...

| Study | Year | Country | Sample size | Age group | Gender (female) | Findings |
|--------------------------------------|------|---------|-------------|-----------|-----------------|--|
| Celiac disease | | | | | | |
| Serratrice et al.* (32) | 1998 | France | 1 | Adult | 100% | Treatment of coeliac disease coincided with total disappearance of severe migraine attacks. |
| Spina et al.* (33) | 2000 | Italy | 1 | Children | 100% | Treatment with three months of gluten free diet, it was obtained the complete resolution of the headache. |
| Roche-Herrero et al. (34) | 2000 | Spain | 86 | Children | NR | An increased prevalence of both migraine and tension headaches was observed in the coeliac patients. |
| Gabrielli et al.* (35) | 2003 | Italy | 236 | Adult | 70% | During the 6 months of gluten free diet, one of the four patients had no migraine attacks, and the remaining three patients experienced an improvement in frequency. |
| Alehan et al. (36) | 2008 | Turkey | 200 | Children | 56.2% | There was an association between migraine and celiac disease. |
| Lionetti et al.* (37) | 2009 | Italy | 554 | Children | 67.5% | The researchers reported a high frequency of headaches in patients with celiac diseases. |
| FrancaVilla et al. (38) | 2014 | Italy | 15 | Children | 33.3% | 20% of patients with celiac disease suffer from headache. |
| Helicobacter pylori infection | | | | | | |
| Gasbarrini et al.* (39) | 1997 | Italy | 225 | Adult | NR | H. pylori is common in subjects with migraine. Bacterium eradication causes a significant decrease in attacks of migraine. |
| Gasbarrini et al.* (40) | 1998 | Italy | 148 | Adult | 66.4% | H. pylori infection is common in primary headache; bacterium eradication appears to be related to a significant reduction in clinical attacks of the disease |
| Tunca et al.* (41) | 2004 | Turkey | 120 | Children | 61.7% | Helicobacter pylori positiveness is more relevant in the migranous patients compared with controls. |
| Yiannopoulou et al. (42) | 2007 | Greece | 39 | Adult | 75.5% | H. pylori infection is a probable independent environmental risk factor for migraine without aura. |
| Hong et al.* (43) | 2007 | China | 50 | Adult | 42% | Intensity, duration, and frequency of attacks of migraine were reduced after H. pylori eradication. |
| Hosseinzadeh et al. (44) | 2011 | Iran | 140 | Adults | 76.5% | Active H. pylori infection is strongly related to the outbreak and severity of migraine headaches. |
| Faraji et al.* (45) | 2012 | Iran | 64 | Adult | 73.4% | H. pylori eradication may have a beneficial role on management of migraine headache. |
| Ansari et al.* (46) | 2015 | Iran | 133 | Adult | NR | H. pylori eradication could be a cure or to reduce the severity and course of migraine headaches. |

*, Studies in which headache was reported to improve or resolve following management of the GI disorder. NR: Not reported.



Spierings reported a 47 year old female patient with chronic constipation complaining of headaches since adolescence. Dietary change targeting the treatment of constipation reduced the frequency of the headaches (2). The Head-HUNT study further demonstrated this association and reported a higher prevalence of headache among individuals with much constipation compared with those without such a complaint (9).

This suggests constipation to be considered in the context of and as a triggering factor for headaches including migraine.

- **Abdominal pain & inflammatory bowel syndrome**

Headaches with migrainous features are reported in 40% of children with functional gastrointestinal disorders (FGID) (24). GI symptoms occurring during migraine attacks such as nausea or vomiting are well appreciated, but there is a growing body of evidence, which points to the occurrence of GI symptoms especially abdominal pain, outside the bouts of headaches (Table 1). A population-based follow-up study investigated the comorbidity of other pains in 513 school-aged children with primary headache and found recurrent abdominal pain to be present in 50% of the patients (19). A large cross sectional study involving 6230 subjects evaluated the prevalence of recurrent complaints in various sites among 7-17 year-old population. The most common pain combination was reported to be headache and abdominal pain (20).

Boccia et al. determined the prevalence of FGIDs in migrainous children and found it to be present in 70% of the patients, among which functional abdominal pain (FAP) comprised 35% of all. This population also suffered from prolonged total gastric emptying time. Treatment with Flunarizine significantly reduced the headaches and GI symptoms (21). FAP in childhood is believed to persist into adulthood in nearly a third of the cases. One study reported that among those with unresolved FAP, headaches are reported to be more prevalent compared to adults in whom childhood FAP did not continue (22). In addition, children with FAP have been shown to suffer more from headache and other non-GI somatic symptoms compared to healthy controls. More than one-third of these children go on to develop FGIDs at follow up as adolescents and adults (23).

One of the most common FGIDs is IBS, which manifests with abdominal pain or discomfort and changes in bowel habits. The comorbidities of this disorder have been widely studied and it is now evident that patients with IBS suffer from a wide range of non-GI symptoms. One of the most appreciated comorbid non-GI symptoms is headache. It has been reported that 30-50% of patients with IBS, complain of headache (Table 1) (25-28, 47, 48). On the other hand, up to 30% of migrainous patients are reported to suffer from IBS. These findings may be explained in two ways. Either migraine or other primary

headaches are not episodic diseases, but in fact they are disorders with underlying abnormality involving other systems that manifest with episodic attacks, or the headaches are manifestations or sequels of disorders in other body systems namely the GI tract.

- **Inflammatory bowel disorders**

Migraine headaches have a higher prevalence in patients with IBD compared to that of the general population (30). Dimitrova studied 111 patients with IBD 23% of which reported chronic headaches and this figure was significantly higher than controls (OR = 2.66; 95% confidence interval [CI]: 1.08-6.54) (31). In Brazil, a prospective study demonstrated headache to be the most common neurological complaint among 82 patients with IBD, 25% of which met the migraine criteria (29). Generalized inflammatory response rather than isolated bowel inflammation may play the key role in the pathogenesis of the extra-intestinal manifestations of IBD (49).

- **Celiac disease**

Also known as non-tropical sprue and gluten-sensitive enteropathy, celiac disease (CD) is now recognized as a multisystem autoimmune disorder characterized by inflammation of the small intestine caused by dietary gluten and related proteins in genetically susceptible individuals (50).

After the publication of case reports introducing migraine as the first manifestation of CD and complete resolution of symptoms following gluten free diet (32, 33), many studies aimed at investigating the association of primary headaches with CD in children and adults (Table 1) (34-38).

Recruiting 188 adult patients with CD and 25 with gluten sensitivity using an ID-Migraine tool, Dimitrova reported chronic headaches to be present in 30% of celiac patients (OR = 3.79; 95% CI: 1.78-8.10) and 56% of patients with non-celiac gluten sensitivity, but only in 14% of controls ($P < 0.0001$) (31). Two studies involving pediatric CD patients were also conducted and similar results to adult studies were reported. In a case control study, contrary to the study performed previously (51), Alehan et al. investigated the presence of tissue transglutaminase IgA antibodies in a group of pediatric migraineurs and found it to be positive in 5.5% of the patients compared to 0.6% of the control group and the difference was statistically significant (36). In an interesting study, Lionetti et al. retrospectively evaluated the prevalence of primary headache (based on the IHS criteria) in 354 children diagnosed with CD. In addition, they prospectively studied the prevalence of CD in a group of pediatric patients with primary headache. In the retrospective phase, they reported headache to be present in 25% of the patients before the diagnosis of CD, compared with eight percent of the control group ($P < 0.001$). In the prospective part, CD was diagnosed by the means of serology and biopsy in 5% of the patients compared with 0.6% of the general



population ($P < 0.005$). Headaches were relieved (and in some completely resolved) after the institution of GFD in patients affected by both conditions (37). Contradicting results have been recently reported in a study, which demonstrates the prevalence of CD in migraine children to be the same as in healthy controls. However, they also showed that GFD improved headaches in the group of children found to have CD (52). Large multicentric studies may resolve these discrepancies.

- ***Helicobacter Pylori Infection***

H. Pylori infection is associated with various extradigestive diseases such as ischemic heart disease, primary Raynaud phenomenon, primary headache, alopecia areata, and hepatic encephalopathy (53). Gasbarrini et al. reported the association of *H. Pylori* infection with primary headache and the improvement of symptoms with eradication of the bacteria (39, 40). Contradictory results were reported afterwards (54, 55), however, more recent studies mainly using histological analysis of gastric mucosa biopsy for *H. Pylori* detection have favored its pathogenic role in migraine (41-44). A double blind randomized clinical trial in 2012, reported the beneficial effects of *H. Pylori* eradication in management of migraine patients (45). Overall, regarding studies supporting a role for *H. Pylori* in migraine it may be judicious to identify *H. Pylori* infection in migraineurs by noninvasive means especially if suffering comorbid GI symptoms.

Pathophysiology

The pathophysiology of headache disorders especially migraine and various GI abnormalities are widely studied individually. However, the scientific literature about mechanisms underlying the comorbidity of the two conditions is scant. Few hypotheses exist aiming to explain the association of headache and GI disorders.

- ***Central sensitization and parasympathetic referred pain:***

Longstanding visceral afferent stimuli on convergent viscera-somatic neurons result in expansion of the receptive fields in size and number, decreased response thresholds, and amplification of response magnitude. This process leads to hyper-responsiveness of neurons within the CNS to nociceptive and non-nociceptive stimuli, which is defined as central sensitization (56).

Dyspeptic migraineurs are shown to have postprandial hypersensitivity to gastric distention. It is postulated that this hypersensitivity in dyspeptic patients, results from abnormal processing of gastric stimuli at the level of the CNS. This in turn activates the common pain network for both somatic and visceral pain, therefore causing headache (14).

The “parasympathetic referred pain” theory is hypothesized for explaining the comorbidity of various GI disorders with headache including migraine. Continuous

stimulus ascending from visceral afferents leads to the central sensitization of trigeminocervical nuclear complex expressing a parasympathetic referred pain in the head (57). Reflux of gastric contents into esophagus in GERD may be one example of chronic visceral stimulus leading to sensitization and referred headache. This theory may also be applicable for patients with IBS, who have various somatic complaints in addition to their GI symptoms. Migraineurs and patients with IBS may have a very sensitive central and enteric nervous system, which have turned hypervigilant through time and may show exaggerated responses to unpleasant stimuli (58).

- ***Serotonin:***

The neurotransmitter serotonin is present in the CNS and in the nervous system within the GI tract. Serotonergic drugs are shown to have regulatory effects on gastric motility, and have been proven beneficial in migraine treatment and prophylaxis. Serotonin hypothesis may therefore be another explanation for the comorbidity of headache and GI abnormalities such as dyspepsia and IBS (14, 59). Serotonergic pathways may represent the target for the treatment of patients suffering from both conditions.

- ***Autonomic nervous system (ANS) dysfunction:***

ANS dysfunction is shown to be present in both headache and GI complaints. The role of ANS is implicated in postprandial gastric accommodation, thus ANS dysregulation may result in delayed gastric emptying and distmotility-like dyspepsia. In addition, migraineurs are demonstrated to suffer from chronic ANS dysfunctions (4, 9, 60) and are noted to have gastric stasis even outside acute attacks (15, 16). This phenomena, however, may be more prominent in migraineurs with dyspeptic symptoms in the interictal period, but interictally symptom free patients, may have normal gastric morphology and accommodation (61-63). The ANS also has a role in the pathophysiology of GERD in which the lower esophageal sphincter is hypotensive or has increased transient relaxations (10).

- ***Calcitonin gene-related peptide (CGRP):***

CGRP is demonstrated to increase during migraine attacks (64-66). This neuropeptide is a potent vasodilator of intracranial vessels (67) and mediates pain transmission in the CNS (68). Infusion of this neuropeptide can induce migraine attack in migraineurs (69). The serotonin receptor agonist sumatriptan, which is administered to manage the acute bouts of migraine, is suggested to act partly by blocking the release of CGRP (70).

In addition, this neurotransmitter helps to regulate gastric relaxations in response to ingestion of food or liquid. CGRP has been shown to have a role in disorders of the gastric reservoir functions leading to functional dyspepsia with anorexia and early satiety (4, 10). CGRP therefore, may have a role in the association of migraine and GI disorders.



- **Vasculopathy:**

Vascular tone dysfunction and abnormal regional cerebral blood flow is demonstrated in migraineurs affected by CD or H. Pylori (35, 37, 42, 71, 72). Since CD arises from an autoimmune response against tissue transglutaminase it is postulated that the same interaction may take place against this enzyme within the brain vascular endothelium leading to various neurologic symptoms observed in patients with CD (36, 73, 74). This theory, however, may be more applicable for adults than pediatric patients (33).

In H. Pylori infection, the immune system interacts with the bacterium and vasoactive agents are released. It is hypothesized that this phenomenon may in turn lead to a systemic vasculopathy and alterations of vascular permeability in various sites including the intracranial arteries. This phenomenon along with the production of oxidants and nitric oxide results in regional cerebral blood flow changes; hence inducing migraine headaches (39, 42, 44). The role of oxidative stress however, has recently been questioned (75).

- **Food Allergy:**

The role of food allergy in the activation of the immune system and subsequent inflammation has been the subject of study for decades (76). Allergy to certain food antigens and the development of IgE and IgG antibodies may lead to an inflammation response which can play a role in the pathophysiology of migraine and IBS (77, 78). It is demonstrated that migraineurs are positive for IgG food allergens more frequently than control subjects and their symptoms may improve with an elimination diet (79). In recent years, studies have focused on the IgG-based elimination diet for migraineurs and also IBS patients and successful results have been reported in the attenuation of symptoms (80-82). This supports the theory that inflammation may play a key role in the pathophysiology of migraine and may help to explain the comorbidity of primary headaches and GI complaints.

The "Persian Medicine"

"Traditional medicine is the sum of all the knowledge and practices used in diagnosis, prevention, and elimination of physical, mental, or social imbalance; relying exclusively on practical experience and observation handed down from generation to generation whether verbally or in writing" (83).

Traditional medicine (TM) is growing more and more popular worldwide (84). The affordability and accessibility of this system along with concerns regarding side effects of chemical drugs and management of chronic debilitating diseases such as cancer, diabetes, and heart disease has led many patients to become more interested in TM (85).

The TM practiced in Iran, called the "Persian Medicine"

(PM), which is known as Greeko-Arabic (Unani) medicine elsewhere (86) has a history of more than 8000 years (87). The underlying physiological concept in PM is that of the "Humoral Theory" which is in coordination with the teachings of the ancient Greek scholars namely Hippocrates (460-370 BC) and Galen (129-199 AD). The Humoral Theory states that there are four types of basic particles from which all elements are made. They act on each other and finally make up the humors, which in turn constitute the body organs. Thus, according to this theory, health results from the balance of humors within the body and their imbalance leads to disease. Humors are four in number named "Dam" (Sanguis or Blood), the quality of which is warm and moist, "Balgham" (Phlegm) which is cold and moist, "Safrā" (Choler or Yellow Bile) which is warm and dry, and "Soada" (Melancholer or Black Bile) which is cold and dry (88, 89).

Medieval medical science was gathered by ancient physicians, the most influential of which were Rāzi (Rhazes, 860-940 AD) and Ebn-e-Sina (Avicenna, 980-1037 AD) and they added to that their own observations and experience (90).

Ebn-e-Sina wrote more than 100 books in his short life span, 16 of which were on medicine (91). His masterpiece the "Al-Qanoon fi al-Teb" (The Canon of Medicine) became the principle medical textbook and was taught and studied in universities of Europe and Asia from the twelfth century until the end of the seventeenth century (92). Partly, statements in this book still have relevance today in different issues of health and disease (93-97). Ebn-e-Sina has described headache disorders and thoroughly discussed the etiology, pathophysiology, symptoms, and various treatments on this issue, in the third volume of the Qanoon.

In this book, headache disorders, referred to as "Soada", are classified into 28 types with each having unique diagnostic criteria and treatment protocols. Some types are classified as headaches originating from different organs which have neurovascular communications with the CNS. One of the most important of these organs was believed to be the stomach, and gastric abnormalities were considered one of the most common etiologies for headache disorders in general (88).

Rāzi also describes in his book the Al-Hawi (Continents), a kind of headache originating from the stomach due to the production of bitter humors in the gastric fundus. Symptoms aggravate during fasting especially after waking up in the morning (90).

Headaches originating from the stomach are classified into seven subtypes. These seven kinds of headache are described here in brief and their key symptoms, aggravating and relieving factors of each kind, are summarized in Table 2.

The first type is headache due to abnormal quality of the



Table 2: The seven types of headache arising from abnormalities within the stomach

| Etiology | Key symptoms | Aggravating factors | Relieving factors | Treatment ^a |
|--|---|---|---|---|
| Abnormal quality of humors | headache occurring after heavy meals | Overeating | Eating less; prokinetics | Restoration of the normal quality |
| Excess Safra (Choler or Yellow Bile) | Nausea; anorexia; bitter taste in the mouth; excess thirst; subicteric sclera; epigastric burning | Starving; Safra producing foods ^b | Avoiding hunger; vomiting the excess Safra ^c | Clearing the stomach from excessive humor |
| Excess Balgham (Phlegm) | Increased salivation; regurgitation; bloating; anorexia; decreased thirst | Overeating; Balgham producing foods ^d | Starving; vomiting the excess Balgham; Sleep; prokinetics | Clearing the stomach from excessive humor |
| Excess Soada (Melancholer or Black Bile) | Food craving; epigastric burning; regurgitation | Anxiety; depression; Soada producing foods ^e | Relaxation; vomiting the excess Soada | Clearing the stomach from excessive humor |
| Excess luminal gas | Frontal headaches; abdominal pain; bloating | Gas producing foods | Avoiding gas producing foods | Elimination of the excess gas |
| Excess vapors | Pounding headaches; vertigo; tinnitus | Vapor producing foods (onion, garlic, pepper, and spicy vegetables) | Avoiding vapor producing foods; consuming coriander after meals | Elimination of the excess vapor; blocking the ascent of vapors to the brain |
| Weakness of the gastric fundus and the cardia | Headache occurs during hunger especially when waking up in the morning; irritability | Starving; walking under the sun while hungry; malodorous smells | Avoiding hunger and having breakfast in time; avoiding CNS stimulants; avoiding malodorous smells | Strengthening the fundus and the cardia |

^a, Treatment methods presented were carried out by appropriate foods and natural drugs.

^b, Spicy and salty foods, foods fried in oil, eggs, nuts, grapes, coconut, honey.

^c, Certain drugs were used to induce vomiting, patients experienced rapid relief of headache afterwards.

^d, Fish, milk, yogurt, cheese, cucumber, tomato, lettuce, watermelon, strawberry, sour cherry, kiwi, drinking water with meals.

^e, Beef, pork, fish, sausages, ham, eggplant, lentil, potato, mushroom, sour tasting fruits, barley, black tea, coffee.

humors within the stomach. Excess warmth, cold, dryness, or moisture of the humors within the stomach may induce headaches. Once the normal qualities are reestablished headache is relieved.

Imbalance of humors within the stomach comprises the second to fourth type. Excess Safra, Balgham, or Soada in the gastric cavity may lead to mucosal injury and gastric dysfunction. Patients with headache due to excess Soada may also present with manifestations of accumulation of Soada within the CNS and therefore, suffer from mood

disorders. Another type is headache due to the production of excess gas as a result of ingestion of gas producing foods such as leguminous seeds. In the first stages, patients may experience epigastric pain just before the initiation of headaches, and once the abdominal pain and bloating is resolved, the headache improves. The sixth type is headache due to the production of excess vapor in the stomach resulting from ingestion of certain kinds of vegetables capable of producing vapors after gastric digestion. The vapors were considered to ascend to the



brain and induce headaches. Patients may also experience anorexia, nausea, and indigestion following the ingestion of such vegetables (Table 2). The seventh type is headache due to weakness of the gastric fundus. The fundus and the cardia have inadequate strength, gastric visceral sensory thresholds are decreased, and patients have gastric hypersensitivity. Patients are also easily irritated in response to unpleasant stimuli (Table 2). Each of these seven subtypes of headache are clearly defined and thoroughly described by ancient scholars in medieval medical resources and treatment regarding each kind is provided (88, 98). The pathophysiology underlying these types of headache is explained in the context of the Aristotle philosophy and the humoral theory. Nevertheless, they may correspond to the neurovascular mechanisms postulated today for explaining the pathophysiology of headache disorders associated with GI abnormalities such as central sensitization, vasculopathy, and alterations in the regional cerebral perfusion. Patients presenting with primary headache associated with gastric dysfunction (especially dyspepsia), if thoroughly questioned, may be recognized to fit in with one of the seven types of headache disorders above. If this is the case, then they may undergo remission with the institution of the appropriate treatment. This is exactly what is taking place today in PM offices in Iran.

Summary

Comorbidity of headache and GI abnormalities has become a subject of interest to researchers in recent years. There is evidence supporting the association of various GI disorders with primary headaches classified by the IHS. In addition to functional GI diseases, IBD and CD along with H.Pylori infection are also reported to be present in a substantial number of patients with headache. Furthermore, there is a growing body of literature demonstrating improvement or resolution of headache following management of the accompanying GI disorder. This raises the idea of existence of a possible unique diagnostic entity in the classification of headache disorders, the "Headache of Gastrointestinal Origin". This was once believed by ancient scholars namely Râzi and Ebne-Sina. They practiced treatment of this kind of headache in their patients and expressed their experiences in their writings. This entity may provide explanation for headaches which resolve following treatments targeting the associated GI disorder. Efforts should be made to clarify this type of headache, however arriving at a strict criteria may be challenging.

Patients fulfilling criteria for any type of primary headaches through the ICHD, should be thoroughly questioned about GI symptoms. If any GI abnormality, either functional or organic, is detected, especially outside the bouts of headaches, treatment targeting the GI abnormality is instituted. Once the GI abnormality is managed,

symptoms of the primary headache are reevaluated. If headaches are improved or completely resolved, the headache would be the one of gastrointestinal origin and the patient may be given the diagnosis of "Headache attributed to GI disorders".

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