



Association between gastrointestinal disorders and migraine: an integrative review

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Abstract

Introduction

Migraine is a highly incapacitating type of primary headache, characterized by high prevalence and symptoms lasting from 4 to 72 hours. It is typically unilateral and pulsatile, often accompanied by nausea, hypersensitivity to sensory stimuli, vomiting and intense fatigue, and it may or may not be preceded by an aura. Although the pathophysiology of migraine is not completely understood, several mechanisms involving the gut-brain axis may explain the association between migraine and gastrointestinal disorders.

Objective

This review aims to analyze the influence of gastrointestinal disorders on migraine.

Methods

An integrative review was conducted by surveying articles in the LILACS, PubMed, and Scielo databases using relevant descriptors related to migraine and gastrointestinal disorders.

Results

The research identified 31 articles, of which only 11 met the previously established criteria. All eligible articles demonstrated a correlation between migraine and gastrointestinal disorders, with Irritable Bowel Syndrome (IBS) being the most frequently mentioned condition.

Conclusion

Gastrointestinal disorders influence migraine, possibly through tryptophan metabolism and its associated pathways. Understanding these mechanisms may lead to new treatments. IBS stands out among the disorders associated with migraine, suggesting an integrative approach. Changes in diet and lifestyle, along with medications, are recommended. Early identification of comorbidities can facilitate more effective migraine management. However, further research is needed to develop more effective treatments.

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Introduction

Migraine is a substantially disabling type of primary headache, characterized by a high prevalence and with symptoms that can last from 4 to 72 hours. It is often unilateral, pulsatile and accompanied by nausea, multisensory hypersensitivity, vomiting and marked fatigue. In addition, around 25% of patients affected by migraine have auras, which usually precede the onset of the headache (1-3). According to the World Health Organization (WHO), approximately half of the adult population has had at least one episode of headache in a year (4).

There are several mechanisms involving the brain-intestine axis that could explain a possible association between migraine and gastrointestinal alterations. These include the inflammatory response with inflammatory and vasoactive mediators circulating through the bloodstream, modulation of the enteric immune response by the intestinal microbiota and dysfunction of the autonomic and enteric nervous systems (5-10).

However, the precise mechanisms related to the brain-intestine axis that trigger migraine attacks need to be fully elucidated. This integrative review explored the available literature on the influence of gastrointestinal disorders in triggering migraine, as well as correlating the pattern of migraine with the prevalence of these disorders.

Methodology

This study adopted a descriptive and exploratory approach, using a bibliographic survey and an integrative literature review. The process was structured in six distinct stages: selection of hypotheses or questions; definition of sample selection criteria; characterization of original research; data analysis; interpretation of results; and presentation of the review.

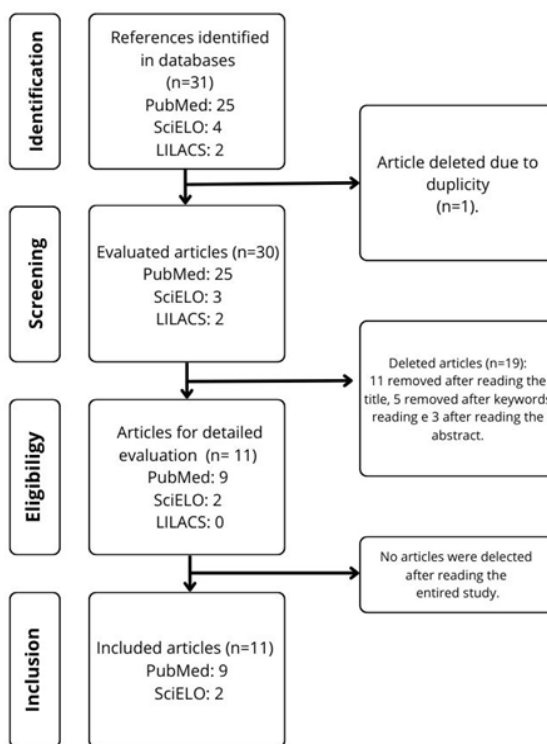
The central question guiding the research was: what is the nature of the relationship between gastrointestinal disorders and the occurrence of migraine in patients? To answer this question, the study conducted a search for articles in the LILACS, PubMed and SciELO databases, using the descriptors "migraine disorders" OR "migraine headache" AND "gastrointestinal disorders", combined in various ways.

Some specific criteria were considered in order to include the articles in the research. The choice was made for articles written in Portuguese or English that addressed the topic. In addition, only studies published and indexed in databases between January 2018 and July 2023 were

selected. On the other hand, the criteria used to exclude articles from the research were repeated articles and those that did not meet the study's objective. The sample was selected by analyzing the title, keywords, abstract and full text.

Results

In the search conducted in the LILACS, PubMed and SciELO databases, 31 articles were initially identified. After careful screening, one article was excluded due to duplication; 11 were removed after reading the titles; five after reading the keywords; and three after reading the abstracts. Finally, the corpus of the integrative review consisted of 11 articles, as shown in the flowchart in Figure 1.



Source: the authors, 2023.

Figure 1. Flowchart showing the research stages.

After reading the 11 articles selected, Table 1 was drawn up to systematize the main information from each study. This Table includes the author, the year of publication, the database in which the article was found, the title and a summary of the overview of each article.



Table 1. Summary of articles used for analysis

Citation and date	Title	Database	Summary of results
Aurora et al., 2021	A link between gastrointestinal disorders and migraine: insights into the gut-brain connection	PubMed	The article discusses the relationship between gastrointestinal disorders and migraine, highlighting the pathophysiological characteristics and symptomatology shared between the two conditions.
Fila et al., 2021	Kynurenine pathway of tryptophan metabolism in migraine and functional gastrointestinal disorders	PubMed	The paper explores possible common triggers for migraine and functional gastrointestinal disorders (FGIDs) through the kynurenine (KP) pathway of tryptophan metabolism, which is involved in the transformation of tryptophan into various neuroactive compounds. The authors suggest that modulating KP could provide a breakthrough in the treatment of migraine and FGIDs.
Martami et al., 2018	Comorbidity of gastrointestinal disorders, migraine, and tension-type headache: a cross-sectional study in Iran	PubMed	The study investigates the relationship between migraine and tension headache and different disorders of the lower and upper gastrointestinal tract, as well as non-alcoholic fatty liver and cholelithiasis in overweight and obese participants. The results show that treating gastrointestinal comorbidities can lead to improvements in migraine in these patients.
Welander et al., 2020	Migraine and gastrointestinal disorders in middle and old age: a UK Biobank study	PubMed	The research addresses the association between migraine and gastrointestinal disorders in middle-aged and elderly individuals. The aim is to determine the relative strength of the associations between migraine and various gastrointestinal disorders, including irritable bowel syndrome (IBS), peptic ulcers, <i>Helicobacter pylori</i> (HP) infections, celiac disease, Crohn's disease and ulcerative colitis. The analysis uses basic data from 489,753 UK Biobank participants, 14,180 of whom have migraine. The results show that migraine was significantly associated with IBS and peptic ulcers, but not with HP infection, celiac disease, Crohn's disease or ulcerative colitis. Thus, the study suggests a weaker link between migraine and autoimmune gastrointestinal diseases or HP infection.
Noghani et al., 2019	Migraine associated with gastrointestinal disorders: a pathophysiological explanation	PubMed	The article proposes a pathophysiological explanation for migraine and its relationship with gastrointestinal disorders, based on the philosophy of Persian medicine and existing evidence. It is suggested that noxious stimuli from the gastrointestinal tract can reach the trigeminal caudal nucleus (TNC) and result in neurogenic inflammation. Histamine, for example, released in the gastrointestinal tract, can make migraine patients more prone to attacks. The authors also highlight the role of mast cells in the pathophysiology of both disorders and suggest that degranulation can be considered a diagnostic marker with high sensitivity and specificity for functional dyspepsia.
Boutrid et al., 2019	"3M": migraine, microbiota and melatonin	PubMed	The paper highlights the interconnection between migraine, gut microbiota and melatonin, suggesting that interventions targeting gut health and microbiota balance, as well as the proper regulation of melatonin, could be promising strategies in the management and treatment of migraine.
Chen et al., 2020	Structural and functional characterization of the gut microbiota in elderly women with migraine	PubMed	The study investigates the relationship between gut microbiota and migraine by analyzing fecal samples obtained from elderly women suffering from migraine and matched healthy controls. The article points to significant differences in the composition and function of the gut microbiota between the migraine and healthy groups, which could help improve the early diagnosis of the disease and provide new therapeutic targets and strategies for the treatment of migraine.
Griauzdaite et al., 2020	Associations between migraine, celiac disease, non-celiac gluten sensitivity and activity of diamine oxidase	PubMed	The research explores the relationship between migraine, celiac disease, non-celiac gluten sensitivity (NCGS) and diamine oxidase (DAO) activity. The authors propose the hypothesis that low serum DAO activity is related to celiac disease and NCGS in the pathogenesis of migraine. In addition, they suggest a strong relationship between reduced serum DAO activity and NCGS in patients with severe migraine.
Parohan et al., 2020	Effect of probiotic supplementation on migraine prophylaxis: a systematic review and meta-analysis of randomized controlled trials	PubMed	The article evaluates the impact of probiotic supplementation on the frequency and severity of migraine attacks. The meta-analysis of the trials reveals that probiotic supplementation has no significant effect on the frequency and severity of migraine episodes.
Ozan et al., 2018	Constipation is associated with tension type headache in women	SciELO	The paper discusses the association between constipation and tension headache in women, finding a high frequency of IBS and headache in this group. The results indicate that these conditions may have common pathophysiological mechanisms. Therefore, the study suggests that doctors should consider the possibility of IBS and other functional gastrointestinal disorders in patients with tension headache, especially among female patients.
Souza et al., 2020	Association between migraine, constipation and lactose intolerance in adults patients	SciELO	The study examines the association between lactose intolerance and constipation in patients with migraine. The sample consists mainly of women and, while there is a considerable prevalence of constipation and lactose intolerance, no statistical significance was found in the association between migraine and these two gastrointestinal disorders.

Source: the authors, 2023.



In the selected articles, various diseases were associated with migraine, including gastroparesis (11), functional dyspepsia (11,12), non-alcoholic fatty liver disease (13), irritable bowel syndrome (IBS) (2,11-15), cyclic vomiting syndrome (CVS) (11,14), celiac disease (2,13), peptic ulcer and infection with *Helicobacter pylori* (HP)(2). Among these conditions, IBS was the most frequently cited, appearing in six of the 11 articles analyzed. Although celiac disease was mentioned in two articles, these did not confirm a causal relationship with migraine. In addition to gluten, lactose was also mentioned as a possible trigger for this headache (16).

Analysis of the data revealed that many studies indicated a possible association between gastrointestinal symptoms, such as diarrhea and constipation, and the exacerbation or modification of the headache pattern (14,15). The intestinal microbiota can influence the development of this condition (2,16-19). In a study using gut microbiota sequencing from fecal samples of elderly women with migraine and controls, a significant reduction in species diversity was observed in the migraine patient group (18). Probiotics have been investigated for their benefit in the treatment of migraine. However, the studies indicated that there was no significant improvement in migraine frequency or severity (18,19).

Discussion

Since the 1980s, significant advances have been made in the pathophysiology and treatment of migraine. However, one of the big questions that remains unanswered is related to the triggering factors of this condition, as well as the challenges in preventing it (20). The frequent association of migraine with symptoms consistent with the diagnosis of functional gastrointestinal disorders (FGIDs) is revealed by several epidemiological studies. The mechanisms behind this association have yet to be clarified, but possible pathways may involve the brain-intestine axis, as well as neuroendocrine and immune-mediated interactions (21).

Recent studies show an increase in the frequency of gastrointestinal disorders in patients with migraine compared to the general population. Conditions such as IBS, gastroparesis, celiac disease, HP infection, hepatobiliary disorders and alterations in the microbiota have been associated with the occurrence of migraine (13,14,22,23).

Among the gastrointestinal disorders associated with migraine, IBS stands out as one of the most frequently related to migraine in studies (3,7,12,15,24). Although the link between IBS and migraine is clear, the mechanisms underlying this association remain unclear. Understanding of the etiology of IBS is still limited, but lifestyle factors appear to have a significant influence. Changes in diet and healthy habits are recommended for patients with IBS,

suggesting an integrative approach to the treatment of these interrelated conditions (7).

In addition to IBS, other conditions such as gastroparesis, functional dyspepsia and CVS were also prevalent in some studies. Di Stefano et al.(25) observed that migraine is a common comorbidity in patients with functional dyspepsia and postprandial symptoms. In their study, 60 patients had functional dyspepsia, 38 with postprandial discomfort syndrome (PDS) and 22 with epigastric pain syndrome (EPS). Of this total, 68% had migraine without aura. Among the patients with EPS, 54% had migraine without aura, which was not correlated with food intake. In contrast, 76% of PDS patients had migraine, and 89% of migraine attacks were correlated with food intake.

With regards to patients with CVS, a study carried out by Fleisher et al.(26) reports that 70% of patients who had an episode of CVS experienced a migraine attack during or between episodes of CVS. In another study conducted by Bhandari et al.(11) in adult patients with CVS (N = 20,952) and patients without CVS matched by age (N = 44,262), migraine was a more commonly observed comorbidity in patients with CVS (9%) compared to patients without CVS (3%). Additionally, it is worth noting that both functional dyspepsia and CVS are part of a spectrum recently classified as disorders of brain-intestine interaction (DGBI) (27).

In the case of gastrointestinal autoimmune diseases, such as celiac disease, Crohn's disease and ulcerative colitis, there is a weaker association with migraine (3,17). The work of Griaudzaitė et al.(17) discusses the enzyme diamine oxidase (EDO), which is responsible for the degradation of histamine, and how variations in the concentrations of its activity can trigger elevations in histamine levels, resulting in allergic reactions, headaches and migraine. This study also shows that histamine intolerance resembles the responses provoked by gluten, suggesting a close relationship between histamine and gluten. However, due to the low number of patients who met the diagnostic criteria for celiac disease, the result was inconclusive.

These findings suggest that the link between migraine and gastrointestinal conditions may not be uniform. This highlights the need for earlier and more accurate identification of comorbidities, which may help in the more effective management of migraine, reducing both the frequency of episodes and the cost of treatment, and thus improving the quality of life of patients (12).

In addition, the gastrointestinal tract is the main site of tryptophan metabolism. Fila et al.(12) highlight the importance of this amino acid in the brain-intestine axis. Its metabolism occurs primarily in the gastrointestinal tract, following three main pathways: the serotonin pathway, the kynurenine pathway and a third pathway



mediated by the intestinal microbiota.

The serotonin pathway plays an important role in the relationship between tryptophan and migraine, with some research pointing to dysregulation of this pathway as a factor in various pathologies. Such dysregulation can affect gastrointestinal motility and the symptoms of gastrointestinal dysfunctions (3,24,27). The kynurenine pathway, in turn, is responsible for the largest part of tryptophan metabolism, converting it into various neuroactive compounds. Research suggests that this pathway may be crucial to the development of new preventive and therapeutic treatments for migraine, due to its ability to directly influence the nervous system (12). Finally, the third pathway involves the intestinal microbiota, which has a profound impact on the brain-intestine axis (28).

Changes in the microbiota can trigger a cascade of effects, including dysbiosis, which has been shown to be relevant in migraine studies (3,12,16,18,19,29). For example, in an analysis of fecal samples, it was shown that patients suffering from migraine have a decreased diversity in the intestinal microbiota, suggesting the use of probiotics as a potential target for the management of this condition (19). On the other hand, in a meta-analysis on the effect of probiotics on migraine, the results were inconclusive in terms of reducing the frequency and severity of episodes (16).

Another study looks at the relationship between melatonin and the intestinal microbiota. The work points out that the human intestine contains at least 400 times more melatonin than the pineal gland. In addition, melatonin receptors in the gut are involved in the regulation of pain, inflammation and motility. The study also reveals that melatonin levels are lower in patients with a history of migraine compared to healthy patients (18).

It should be noted that diet is a key regulator of the intestinal microbiota (30-32). Changes in diet can explain more than 50% of the variations in the microbiota compared to genetic alterations that explain only approximately 10% of the variation (33). As noted by Peatfield et al. (34), diet has long been a known factor in triggering migraine.

Probiotics represent another potential therapy for migraine because, as dietary interventions, they can alter the intestinal microbiota (28). In a double-blind randomized controlled study, Martami et al.(7) observed that patients with chronic migraine who received probiotic treatment for eight weeks showed a significant reduction in the severity, frequency and use of medication for this disease compared to placebo controls.

Finally, about lactose intolerance, Souza et al.(29) reported that lactose intolerant patients had a longer average migraine time (19.9 ± 14.2) compared to lactose tolerant

patients. However, although the average was higher in the intolerant patients, the study states that there was no statistical significance in the association of migraine with lactose intolerance.

Conclusion

Gastrointestinal disorders seem to have a major influence on the etiology of migraine. The metabolism of tryptophan and its associated pathways, including the serotonin and kynurenine pathway, as well as the role of the intestinal microbiota, are possible pathophysiological mechanisms that interfere with the brain-intestine axis. Understanding these mechanisms could provide crucial information for the development of new preventive and therapeutic treatments for migraine.

IBS has emerged as a prominent condition among the gastrointestinal disorders associated with migraine, highlighting the importance of an integrative approach in the treatment of these interrelated conditions. The promotion of a healthy lifestyle and dietary changes are recommended, as they play an important role alongside drug treatment.

Early and accurate identification of comorbidities can facilitate more effective management of migraine, resulting in a substantial improvement in patients' quality of life. However, further research is needed to better understand these connections and develop more effective treatment strategies.

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