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Migraine associated with gastrointestinal disorders: A pathophysiological explanation

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ABSTRACT

Background: Migraine is a highly prevalent, disabling, and costly disorder worldwide. From a long time ago, headaches have been known to be associated with gastrointestinal (GI) disorders. Headaches originating from gastric complaints were appreciated by Persian Medicine (PM) scholars. Today, functional GI disorders are shown to have high comorbidity with migraines; however, a causal relationship is not accepted today and pathophysiological explanations for this comorbidity are scarce. Therefore, based on the PM philosophy and the existing evidence, we aimed to propose an explanation for the co-morbidity of migraine and GI disorders.

Summary: Noxious stimuli from the GI tract are relayed to the nucleus tractus solitarius (NTS) in the brain stem, which is located close to the trigeminal nucleus caudalis (TNC). TNC has shown projections to (NTS) through which frequent GI stimuli may antidromically reach the TNC and finally result in neurogenic inflammation. In addition, immune products, particularly histamine, are released in the submucosa of the GI tract and absorbed into the systemic circulation, which renders migraineurs more prone to attacks.

Introduction

Epidemiology

Primary headache disorders are highly prevalent worldwide. The global figure is 46% for headache in general, 11% for migraine, and 42% for tension-type headache [1]. In addition, as reported recently, migraine now is the sixth most prevalent disorder and stands as the second most disabling disease in the world [2]. Migraine disorders have a negative economic impact on the community. The mean total annual headache-related costs for patients in the USA is $1533 for episodic migraine and $4144 for chronic migraine [3]. For patients in various European countries, this figure ranges from €486 to €1092 for episodic migraine and from €1495 to €3718 for chronic migraine [4].

Association of headache and GI disorders

For a long time, the association of migraine and gastrointestinal (GI) disorders has been recognized by medical practitioners as a matter of cause and effect. Migraine arising from GI complaints was appreciated as a distinct entity throughout the medieval era up to the beginning of the 20th century [5]. Afterward, this clinical entity was neglected for unknown reasons and, today, except for “8.1.5 dietary headache”, no such classification is accepted in the international classification of headache disorders (ICHD-III) [6]. However, the association of GI and primary headache disorders has regained attention in recent decades [7] and evidence regarding the co-morbidity of the two disorders is growing in the literature [8–10].

Despite the abundant evidence, a widely accepted pathophysiological explanation to delineate a causal relationship for this association is not yet made. However, a number of factors are assumed to have a role in the pathophysiology of both disorders. These include immune cells namely mast cells (MCs), and central-enteric nervous system interactions. Herein, with respect to the available evidence and the historical medical view, we aim to propose an explanation for the co-morbidity of migraine and GI disorders.

Persian medicine

In Persian Medicine (PM), formerly known as the Iranian Traditional Medicine (ITM), Headache disorders (Sodae) are categorized roughly into 27 classes, some types of which are still relevant today. One category mentioned in PM is headache disorders caused by diseases of the extra-cranial organs, particularly of the GI system [11]. Stomach was known to be highly innervated and interrelated with the brain. The mechanism through which the GI may cause headaches was

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thought to be neurovascular. The sixth pair of nerves descending from the brain, today known as the cranial nerve X or the Vagus nerve, was considered responsible for the association of headaches and gastric disturbances. Moreover, vapors ascending from the stomach were known to be capable of triggering headaches. Vapors are delicate material made up of each of the four humors that are able to penetrate soft tissues, bony surfaces, blood, and lymphatic circulation. Therefore, vapors produced in the stomach and the gut were believed to reach the cranium and influence the brain activity. The term “Gastric Headache”, once recognized in the literature, points to this historical belief [12].

Migraine pathophysiology

The pathophysiology of migraine includes Trigemino Vascular System (TVS) activation and neurogenic inflammation [13]. The inflammation within the meninges leads to peripheral and later, central sensitization; and thus pain chronification. Activation of the TVS may start from triggers acting on the trigeminal nerve. Depolarization of the trigeminal nerve may transmit neural signals either orthodromically to the Trigeminal Nucleus Caudalis (TNC) for pain perception, or antidromically to the dura mater to inflame the meningeal tissue and vascular bed. Activation of trigeminal nerve endings in the dura mater results in the release of neuropeptides particularly substance P, nitric oxide, and Calcitonin Gene-Related Peptide (CGRP), which are potent vasodilators and may activate nearby mast cells (MCs).

MCs may then degranulate and release various vasoactive and chemoattractant agents such as histamine, vasoactive intestinal polypeptide (VIP), and nitric oxide, which in turn may recruit other immune cells; hence, the neurogenic inflammation worsens and trigeminal nerve stimulation may continue [14]. MCs play a critical role in the generation and maintenance of dural inflammation. Experimental studies have demonstrated the inhibition of neurogenic inflammation after trigeminal stimulation in MC-deficient mice [15] or following pretreatment with MC stabilizers [16]. This shows the important role of MCs in the generation of migraine headaches.

One of the most effective MC mediators is histamine. Histamine is a biogenic amine with potent vasodilatory properties, the intravenous infusion of which may induce migraine headaches [17]. The plasma level of histamine has been shown to be significantly elevated in migraineurs compared to healthy controls [18]. Moreover, histamine free diet may set migraine sufferers headache free [19]. These all point to the critical role of histamine and MCs in the pathophysiology of migraine.

The underlying pathophysiology of some GI disorders

Visceral hyperalgesia and autonomic dysfunction, immune activation and inflammation, epithelial barrier disruption, and microbiota alteration are important pathophysiological mechanisms in functional and non-functional GI disorders [20–22].

CNS-ENS interactions; peripheral and central sensitization

The enteric nervous system (ENS) consists of millions of neurons distributed in different layers of the GI tract wall. The ENS is connected to the central nervous system (CNS) via parasympathetic and sympathetic fibers. Mechanical and chemical stimulations are perceived by numerous nerve terminals, the number of which reaches nearly 50,000. They transmit through afferent fibers to the spinal cord and the brain stem [23]. Stimulations may come from food particles, various antigens, toxins, microbial products, immune system products, and GI wall tensions, which all finally are delivered to the brain stem. In the brain stem, the Nucleus Tractus Solitarius (NTS) receives sensory data from GI afferents. Afterward, through reflex arcs to the Dorsal Vagus Nucleus, efferent fibers may be activated to regulate GI motility and secretion [23]. In addition, after reaching the NTS, afferent GI sensory data are eventually relayed to the sensory cortex and the limbic system so that the brain is made aware of GI feelings including hunger, satiety, pain and discomfort, fullness, and nausea, while mood and emotions are also affected [24].

In inflammatory states, noxious stimuli such as pain are frequently delivered by afferent fibers to the CNS. Repetitive stimulation and frequent firing of the afferent nerves renders them sensitized, which is known as peripheral sensitization. Frequent pain transmission to the CNS eventually leads to central sensitization and subsequent hyperalgesia of the GI tract, which is the mainstay of symptoms in functional GI disorders. Irritable Bowel Syndrome (IBS) patients along with dyspeptic patients frequently report hyperalgesia and visceral hypersensitivity, which is the result of central sensitization [25].

Immune activation; the role of mast cells

MCs are unique immune cells that are activated by several non-immune factors and play a role in the development of various inflammatory diseases in the nervous, cardiovascular, GI, urinary, musculoskeletal systems, and the skin [26].

In the GI tract, MCs are normally present in the mucosa and play a role in preserving immunity. They communicate with cells and nerve fibers in their surrounding environment [27]. Their function is to regulate epithelial and vascular permeability, ion exchange, angiogenesis, peristalsis, tissue repair, immune cell function, bacterial defense, and pain perception. Thus, MCs malfunction may lead to GI homeostatic disturbance and inflammation and, hence, organic and functional disorders may ensue [28].

Functional GI disorders (FGIDs) are now considered not to be purely functional. Micro-inflammation is demonstrated to contribute to the development of functional dyspepsia (FD) and irritable bowel syndrome (IBS) [20]. In FD, MCs and Eosinophils are found in great numbers in gastric and duodenal mucosa, which may compromise the microenvironment and result in organ dysfunction. MCs are shown to be in close proximity with nerve endings in the GI mucosa. Therefore, MC degranulation in response to gastric distension or exposure to food antigens may expose the ENS and GI musculature to a variety of biogenic active substances resulting in dyspeptic and irritable symptoms [27]. Available data suggest that dyspeptic symptoms are correlated with the presence of MCs. H.pylori eradication per se may not always lead to symptom resolution in dyspepsia. Increased MC infiltration in gastric and duodenal mucosa in patients with dyspepsia may lead to postprandial fullness, pain and discomfort, delayed gastric emptying, and also extra-digestive symptoms such as anxiety and depression [27,29–32].

Studies on patients with functional dyspepsia (FD) point to the fact that gastric and duodenal mucosal and submucosal MCs are necessary for symptom generation. Therefore, MC degranulation could be regarded as a diagnostic marker with high sensitivity and specificity for FD [33].

Studies on patients with IBS reveal that the number of MCs in the mucosa of their GI tract from duodenum down to the rectum is 1.2–2.5 times higher than healthy subjects [20].

MCs are located close to the nearby nerve endings in the mucosa of the GI tract [34]. thus, the frequent release of MC mediators may gradually sensitize the sensory nerves, reducing their activity threshold and leading to visceral hypersensitivity and hyperalgesia. In addition, increased nerve activity may again render the mucosal MCs to neuropeptide exposure, MC activation, and subsequent inflammatory cell recruitment. Therefore, factors precipitating MC activation including food particles, antigens, infection, microbial products, microbiota alteration, and stress may all eventually lead to GI tract chronic inflammation and subsequent functional disturbance.

Explanation of the association between headache and GI disorders

NTS-TNC

Several functional and organic GI disturbances including FD, IBS, GERD, IBD, and Celiac disease, which involve mucosal irritation and/or chronic inflammation, involve the frequent transmission of noxious neural impulses from the GI tract to the CNS. NTS is one of the main centers in the CNS for receiving sensory afferent nerves of the GI tract [24]. This nucleus receives parasympathetic and also sympathetic impulses from the GI tract. NTS is located close to the TNC, the largest brainstem nucleus extending from the mid-brain down to the upper cervical portion of the spinal cord. The TNC receives sensory data from several parts of the head, including the face, scalp, and meninges. TNC has extensive connections with several nuclei in the brainstem. One of these connections is the NTS [35–37]. Central sensitization mediated by repetitive unpleasant GI stimuli may result in receptive field expansion, decreased activation thresholds, and increased response magnitude [38] in the NTS. Consequently, via NTS-TNC inter-connections, the TNC may also receive frequent impulses. TNC activation may, through antidromic conduction, result in neurogenic inflammation in the dura mater and, therefore, headache disorders ensue. This neural pathway could serve as one proposed explanation for the co-morbidity of GI disorders and primary headache disorders. In these patients, the brainstem (CNS) is more sensitive and the trigeminovascular system is more prone to activation [39]. Hence, patients with GI disorders suffer more commonly from headache disorders [7].

Histamine

Since MCs in the GI tract are located near peptidergic nerve fibers and endothelial cells [40,41], their degranulation may influence the ENS, the GI blood flow, and the blood-gut-barrier (BGB). After MC activation, substances released may pass through the BGB and enter the systemic circulation [42].

Because MCs contribute to the pathophysiology of both migraine and GI disorders and these two conditions are significantly associated with each other, MCs may be accounted for a common pathophysiologic factor in both disorders. A large proportion of histamine in the body is produced by MCs. It may be proposed that MCs, which have infiltrated the GI tract in various GI disorders, may release a high amount of histamine that acts locally and eventually enter the systemic circulation. Consequently, the elevated plasma histamine level may set patients more vulnerable to headache attacks [43].

Collectively, it could be concluded that the inappropriate presence of MCs in the GI tract may give rise to GI symptoms and dysfunction. In addition, The release of MC bioactive substances namely histamine may by (a) a paracrine fashion, influence the ENS-CNS axis, and by (b) an endocrine manner, stimulate the meningeal vasculature and activate the TVS.

Conclusion

Migraine has proved to be highly associated with GI disorders. From the traditional point of view, the GI system can be the source of headaches through neurovascular routes. We hypothesize that the GI tract may influence the TVS and induce neurogenic inflammation via nervous connections (NTS-TNC) and systemic circulation (histamine). Therefore, it is recommended paying full attention to treating the GI disturbance in the management of headache disorders. Recognizing primary headaches that have comorbidity with GI disorders as a distinct entity in ICHD, may help to appreciate the importance of treating the comorbid GI disturbance.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Declarations of interest

None.

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