Migraine Comorbidities

Subjects: Neurosciences

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Migraine is a primary headache, with a high prevalence and morbidity among young adults, especially women, that significantly reduces the quality of life. Approximately 1 billion people worldwide suffer from migraine and this disorder remains the second leading cause of disability worldwide, after low back pain, despite considerable progress in diagnosis and treatment. The incidence of migraine attacks peaks between early and mid-adolescence, although attacks can occur at any age.

migraine comorbidities epilepsy anxiety and mood disorders CGRP gut–brain axis microbiome

1. Epilepsy and Migraine

Over time, there has been an association between epilepsy and migraine. This means that seizures can trigger migraines and that migraine attacks could have an epileptogenic component [1]. Migraine is estimated to be 8–24% prevalent in populations with epilepsy, which means that migraine risk is approximately twice as high as in the general population. At the same time, people with migraine have a higher incidence of epilepsy (range 1–17%) than the general population (0.5–1%) [1][2][3][4].

In 2004, the International Headache Society proposed the criteria for migralepsy: 1—criteria for migraine with aura and 2—a seizure that occurs during or within 1 h after a migraine aura. However, few cases have been described in the literature and the relationship between these two has not been clarified [4].

The underlying mechanisms that trigger migraine attacks have been studied over time, and similarities have been found between them and those that trigger seizures with focal onset. The phenomenon of cortical spreading depression (CSD) was studied with functional imaging in people that experience migraine aura and transgenic animal models of familial hemiplegic migraine. There is a characteristic feature of CSD in migraine: a depolarization block after hyperexcitability that induces long lasting neuronal depression. Similarly, depolarization block is observed in ictal, interictal, and postictal epileptic activity [5].

CSD causes trigeminal-vascular system activation, with subsequent vasoactive peptides releasing in leptomeningeal space. These peptides (CGRP, substance P) induce vasodilation and sterile inflammation with pain [6].

After convulsions and after cortical spread depression, which is the neuronal mechanism of the migraine aura, there is an increase in extracellular glutamate, an excitatory neurotransmitter. After CSD, the trigeminal nucleus is involved with consequent central sensitization and pain; headaches and migraine aura may trigger seizures in epilepsy patients [7].

Glutamate is also an excitatory neurotransmitter implicated in aberrant signaling from epilepsy. Extracellular glutamate increases after seizures and has excitotoxic effects [8].

In everyday practice, visual symptoms associated with occipital seizures are sometimes mistaken for visual auras in migraine, despite the fact that they tend to display typical characteristics that distinguish them from migraine. Although EEG studies are not useful for routine headache evaluation, 24 h video-EEG studies in isolated cases with migralepsy showed EEG changes not typical of epilepsy during the migraine aura; moreover, epileptic ictal headaches do not have a specific pattern [6].

Several gene mutations associated with familial hemiplegic migraine type 1 (FHM1) and FHM 3 have been described. In familial hemiplegic migraine 1 (FHM 1), there are genes that encode P/Q calcium channels in FHM 3 for voltage-gated sodium channels. These mutations are likely to be responsible for an increase in neuronal glutamate [9]. There are *SCN1A* mutations with both FHM and epilepsy, like L263Q, T1174S, Q1489H, and L263V. As a result of the L263V mutation, sodium channel inactivation is accelerated, thus prolonging the duration of action and increasing neuronal excitability. A patient with this gene mutation may have epilepsy and FHM3 [10][11].

Another studied gene is *CACNA1A* that encodes a subunit of the P/Q calcium channel. Its mutation may damage calcium channel function and cause generalized epilepsy or FHM [1][11].

Apart from genes in FHM that encodes ion channels, there are genes such as *ATP1A2* that regulate membrane potential and inhibit Na^+/K^+ ATP-ase. As a result, migraine seems to be fundamentally a disorder of altered neuronal excitability in a similar way to epilepsy [11][12].

Another link between migraine and epilepsy is that anti-seizure drugs (ASD) can prevent migraine attacks. Perhaps this treatment involves peripheral dural or central trigemino-vascular mechanisms. Studies on animals have shown an inhibition of neuronal firing in the trigeminocervical complex and modulation in trigeminovascular transmission after intravenous topiramate [13][14]. Topiramate also inhibits the CGRP secretion from activated trigeminal neurons and may target cortical spread depression [15].

Another ASD used in migraine prophylaxis is valproate through GABA activity enhancement. In this way, there is a suppression of migraine events from the cortex, perivascular parasympathetic, and trigeminal nucleus caudalis [16].

There are also other studies of ASD in migraine prophylaxis like levetiracetam, lamotrigine, and gabapentin. Levetiracetam has a modulatory effect on GABAergic system and one study with the help of magnetic resonance spectroscopy proved a low GABA level in posterior cingulate cortex in persons with migraine that received levetiracetam monotherapy [17][18].

According to some authors, there is no direct cause-and-effect link between migraine and epilepsy. There is a high probability that they are both caused by overexcitation of cortical neurons. In epilepsy, cortical hyperexcitability leads to abnormal hypersynchronous electrical discharges, while in migraine, this hyperexcitability leads to cortical spread depression. In epilepsy, hyperexcitability alters ion exchange processes across membranes, leading to recurrent seizures, whereas in migraine, extracellular glutamate concentrations rise, resulting in an efflux of K+ ions, further affecting neuronal activity and resulting in brain hyperactivity [19].

Patients with both migraine and epilepsy experience symptoms sporadically and the interictal interval between symptoms varies. An alteration in the structure of ion channels can lead to an influx of pathological signals, such as seizures and migraines, to overcome homeostatic mechanisms. In epilepsy, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors mediate seizure generation and spreading; in migraine, N-methyl-D-aspartate (NMDA) receptors are involved in CSD phenomenon [1].

2. Depression, Anxiety and Migraine

Anxiety and depression are two of the most prevalent comorbid conditions associated with migraine, impacting disease prognosis, treatment, and clinical outcome. Researchers have found that people with migraines are five times more likely to develop first-onset major depression than those without migraines. At the same time, the risk of first-onset migraine is three times higher for people with a lifetime depressive disorder than for those without it [20].

The likelihood of suffering from anxiety and suicidal tendencies is higher among migraine patients, especially chronic migraineurs [21].

There is a bidirectional relationship between migraine and anxiety disorders, with one increasing the risk of the other. There are three types of anxiety disorders most often associated with migraine: panic disorder (PD), generalized anxiety disorder (GAD), and obsessive compulsive disorder (OCD) [22]. Animal models were used to investigate the relationship between migraine and anxiety. Studies on the cognitive aspects of headaches in animals have been limited. It is possible to assess pain in different aspects with the help of behavioral tests, including sensory-discrimination, affective-emotional, and cognitive tests [23].

The premonitory phase of migraine includes the activation of the posterior and lateral hypothalamus and midbrain ventral tegmentum. Homeostasis alterations that trigger migraines and some of the symptoms during this phase can be explained by the limbic system's connections [24].

Some current data regarding pathogenesis of anxiety disorders are related to a "threat circuit" in the brain represented by connections between dorsomedial prefrontal cortex, insula, and amygdala. Anxiety disorders are associated with an increased activation of this circuit in response to threatening stimuli [25]. Rodents' emotionality was initially measured with the open-field test. Rats have an aversion to novel, brightly illuminated, open environments, which is the basis of the test. Anxiety is evaluated primarily using the percentage of inner zone distance (ID%) and the percentage of inner zone time (IT%). In anxious rats, ID% and IT% are lower because they

are afraid of exploring and prefer to stay in a safe place, such as the outer perimeter of the open field. According to Bogdanov et al., an open field test was used to assess the correlation between susceptibility to CSD, the most common cause of migraine aura, and anxiety, and they concluded that increased anxiety-like behavior was correlated with a higher frequency of CSD [26].

The limbic system structures are highly sensitive in a patient with chronic migraine because the neuronal hyperexcitability occurring in these areas and neighboring regions causes them to be highly sensitive. It is likely that this sensitization is responsible for the provocation of anxiety disorders when confronted with noxious stimuli [27].

Migraines and anxiety disorders are also often associated with dysfunctions of the serotonergic system. Serotonin (5-HT) metabolism can be altered in migraine patients as well as anxiety patients who have serotonin transporter gene polymorphisms [27][28].

By involving the serotonergic system, the microbiota and gut–brain axis can cause both migraine and depression to coexist. There are several ways in which the gut microbiota can affect brain function, including modulating serotonergic, noradrenergic, dopaminergic, glutamatergic, and GABAergic neurotransmission in the brain [29]. The gut microbiota also contains enzymes that regulate the metabolism of tryptophan, which leads to the production of serotonin, kynurenine, or indole derivatives. The microbiota can influence the brain's production of serotonin [30].

Studies in mice have shown that probiotics reduced anxiety- and depressive-like behavior. Dopamine and serotonin levels in the striatum were significantly increased after chronic Lactobacillus plantarum administration [31]. Lactobacillus brevis non-live strain application stimulated serotonin receptors in intestinal cells, suggesting non-viable microorganisms may also modulate gut–brain axis [32].

An epidemiologic study in France has concluded that people with migraine and anxiety have a lower quality of life, as well as having a higher level of disability when they suffer from comorbid anxiety. They found that 50.6% of subjects with active migraine had anxiety (28.0%) or depression (3.5%) or both (19.1%). There was a lower level of satisfaction with acute treatment among migraine patients with comorbid anxiety than among migraine patients without comorbid anxiety and depression [33].

The relationship between migraine and depression was studied with the help of neurotransmitters and receptors. These two disorders are linked by the imbalance of serotonin (5-HT) neurotransmitters, as evidenced by the response to 5-HT regulators like triptans and selective 5-HT reuptake inhibitors (SSRIs) [34]. Depression has been associated with the monoamine neurotransmitter hypothesis, where there is a decrease in the concentration of monoamine transmitters. Although migraine and depression are linked to dysfunction of monoamine transmitters, the specific mechanism remains unclear. 5-HT levels in migraine patients were found to be chronically low [34][35].

A link exists between migraines and mood disorders in relation to estrogens and their receptors in the hypothalamus. In humans, modulation of the hypothalamic–pituitary–adrenal (HPA) axis and limbic system has

been linked to mood disorders and migraine [36]. When administered before menstruation, cutaneous estrogen supplementation, such as the patch or gel, has been shown to reduce migraine symptoms and regulate migraine activity [37]. In the available research, estrogen has been shown to be pharmacologically effective in reducing depression symptoms [38].

The pivotal role of CGRP in migraine's pathology has been previously discussed. There are studies that found a reduction in depressive symptoms in migraine patients after 3 months of treatment with anti-CGRP medication [39]. In spite of the exhaustive study of CGRP's vasodilation and inflammation activity in migraine, its role in depressive-like behaviors has remained unclear. A CGRP infusion performed intracerebroventricularly induces anxiety behaviors and improves learning and memory. Researchers have found that patients with depression have altered levels of CGRP [40][41]

It has been found that patients with chronic migraine suffer from significantly elevated serum CGRP levels, even when they do not have migraine attacks [42]. Monoclonal anti-CGRP (ligand or receptor) antibodies reduce the severity of depressive symptoms in migraine patients, regardless of migraine reduction. The improvement of depressive symptoms can be a sign that erenumab is providing treatment benefits in migraine [39].

In addition to their shared genetic background, depression and migraine share genes from the serotoninergic, dopaminergic, and GABAergic systems, as well as variants of the MTHFR (methylenetetrahydrofolate reductase) and BDNF (brain-derived neurotrophic factor) genes. However, the characterization of migraine patients with comorbid depression requires larger studies [43].

3. Migraine, the Gut–Brain Axis and Irritable Bowel Syndrome

As the name suggests, the gut–brain axis refers to the bidirectional communication between the gut and the brain, which integrates immunological, neural, and hormonal signals [44]. The microbiota influences many systems and organs in the human body, including the brain. In migraine pathophysiology, the gut–brain axis plays an important role and gut microbiota are crucial in modulating this link, but the exact mechanisms are unclear [45][46]. This connection suggests that modulating the microbiota could play a significant role in migraine treatment and represents a promising research area [45].

Lanza et al. and Kang et al. found preclinical evidence of microbiota involvement in migraine in animal models. A study by Kang et al. shows that gut microbiomes play a vital role in mechanical pain sensation and migraine pathogenesis. A study by these authors found increased basal mechanical sensitivity, as well as no further hyperalgesia induced by NTG (Nitroglycerine) administration. By restoring the gut microbiota, basal mechanical hyperalgesia and hyporesponsiveness to NTG were reversed. Additionally, fecal microbiome transplantation (FMT) successfully reproduced migraine-like pain susceptibility in mice. Lanza M et al. demonstrate that SCFAs play a significant role in migraine pathogenesis, as well as in microbiota composition and intestinal permeability. As a result of NTG-induced migraine in mice, sodium propionate and sodium butyrate significantly restored intestinal

permeability and integrity, as well as the composition of the intestinal microbiota. Through bacterial metabolism of dietary fiber, sodium butyrate (SB) and sodium propionate (SP) are naturally produced in the body. Through the promotion of a healthy gut microbiota, SB and SP may play a role in the prevention of migraines [47][48].

There are many factors that contribute to migraine attacks, including proinflammatory factors, gut microbiome composition, neuropeptides, serotonin pathways, stress hormones, and dietary factors [49].

The gut microbiota, which includes Bacteroides and Firmicutes, is a complex, dynamic system influenced by diet, lifestyle, infections, antibiotic therapy, and hormones [45]. In addition, early life experiences, such as delivery and breastfeeding, are crucial for the development of this complex system [49]. Vagal nerves, tryptophan metabolites, and short-chain fatty acids (SCFAs) act as links between microbiota and the brain [50]. The metabolism and neurotransmission of migraine patients may be altered compared to those without migraine [46].

The gut–brain axis can be affected by dysbiosis, which can contribute to the chronicity of migraine pain by up-regulating TNF-α level in the trigeminal nociceptive system [51]. Microbial dysbiosis may be related to diet, alcohol dependence, smoking, obesity, proton pump inhibitors, selective serotonin reuptake inhibitors, and antibiotic therapy [45].

There are bacteria associated with a healthy microbiome that produce short-chain fatty acids (SCFAs, namely: butyrate, propionate, and acetoacetate), while those that are considered negative in the microbiome are potential pathogens and produce bacterial toxins such as lipopolysaccharides (LPS) [52].

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