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Iron in the migraine brain

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Summary. Iron, a vital element for numerous peripheral and central nervous system functions, is a key player in DNA synthesis, gene expression, myelination, neurotransmission, and mitochondrial electron transport. Iron has utmost importance in various neurological functions, including neurotransmitter synthesis and brain cell metabolism. Migraine is a neurogliovascular disorder in which neuroinflammation plays a crucial role. Iron deficiency has been associated with various neurological issues and could potentially influence migraine frequency or severity. However, the relationship between iron levels and migraine is not fully clear and necessitates further research. On the other hand, iron overload could also have negative effects, as excessive iron might contribute to oxidative stress and inflammation, which may impact migraine-related pathways. The interplay between iron levels and neuroinflammation might affect migraines. While iron deficiency could exacerbate inflammation or disrupt neurotransmitter balance, iron overload might increase oxidative stress and neuroinflammation. Comprehending this balance is fundamental, as both iron deficiency and overload can have detrimental effects on brain health and migraine symptoms. In this review, we will summarize the current interconnection between migraine, iron levels, and neuroinflammation that are currently under active investigation.

Key words: Migraine, Iron, Neuroinflammation, Mitochondrial dysfunction, Brain energy metabolism

Introduction

Iron, a vital element for numerous peripheral and central nervous system (CNS) functions, is a key player in DNA synthesis, gene expression, myelination, neurotransmission, and mitochondrial electron transport. Its role in the structure and function of many enzymes is indispensable. With 60-70% of the body's iron stored in hemoglobin and erythrocytes, 10% in myoglobin and cytochromes, and 20-30% in the liver and reticulo-endothelial system macrophages, the significance of iron in our system cannot be overstated. However, excessive free cytosolic ferrous iron accumulation can lead to oxidative stress and cytotoxicity, underscoring the delicate balance of this essential element (Chifman et al., 2014).

Iron likely enters the CNS through the endothelial cells of the blood-brain barrier (BBB) and the epithelial cells of the choroid plexus, using several of the same transporters identified in the duodenum. Studies have revealed that iron is a crucial player in the synthesis of key neurotransmitters such as serotonin, dopamine, and norepinephrine, which have roles in migraine headaches. This review focuses on the relationship between iron metabolism, excessive iron, iron deficiency-related neuroinflammation, and migraine pathophysiology.

Iron metabolism: Key players and pathways

Iron is present in the diet in organic and inorganic forms. Heme iron is the organic form that originates from hemoglobin and myoglobin via consuming meat. The inorganic iron comes from non-meat sources. The absorption pathways of the two forms are different. Hemoglobin in meat is broken down into heme and globulin by intestinal enzymes in the intestine. Heme iron is in the ferrous (Fe II) form and enters the duodenal enterocyte via heme carrier protein 1. Most of the non-heme iron absorption is ferric (Fe III) iron. The first step

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Abbreviations. CNS, Central Nervous System; BBB, Blood-Brain Barrier; CSF, Cerebrospinal Fluid; IDA, Iron Deficiency Anemia; MAO, Monoamine Oxidase Enzyme; 5-HTP, 5-hydroxytryptophan; CSD, Cortical Spreading Depression; ERK, Extracellular Signal-Regulated Kinase; BDNF, brain-Derived Neurotrophic Factor; CREB, cAMP-Responsive Element Binding Protein; TNC, Trigeminal Nucleus Caudalis; mPTP, Mitochondrial Permeability Transition Pore; PAG, Periaqueductal Gray; CM, Chronic Migraine; EM, Episodic Migraine; NAC, Nucleus Accumbens; sTWEAK, Soluble Tumor Necrosis Factor-Like Weak Inducer of Apoptosis; QSM, Quantitative Susceptibility Mapping

in the absorption is the reduction of Fe III iron to the Fe II form by cytochrome b. Fe II is taken into the enterocyte by divalent metal transporter 1 located on the surface of the enterocyte facing the lumen. İron taken into the enterocyte is stored as ferritin. If it is needed, it is transported to the basolateral side of the enterocyte. It is loaded onto transferrin in the plasma with ferroportin. Fe II must be oxidized to Fe III by hephaestin (Fig. 1) (Rouault et al., 2006).

In the brain, iron entry depends on interactions between endothelial cells and astrocytes. Brain endothelial cells express transferrin receptor 1 on their luminal membrane, bind iron-loaded transferrin, and internalize it in endosomes. Fe III iron is released from transferrin within the endosomes, and endosomal reductases reduce Fe III to Fe II iron. Transferrin is the primary source of iron for neurons. In oligodendrocytes, transferrin may be important in intracellular iron transport along their processes. Fe II iron can bind to adenosine triphosphate or citrate in astrocytes, released and transported as non-transferrin-bound iron. Ferritin is also present in axons and may transport iron to the synapse, and ferroportin in synaptic vesicles may release ferrous iron at the synapses (Fig. 2) (Moos et al., 2007; Rouault, 2013).

Iron likely enters the CNS through the endothelial cells of the blood-brain barrier (BBB) and the epithelial cells of the choroid plexus, using many of the same transporters identified in the duodenum (Moos et al., 2007; Rouault, 2013). Unlike the capillaries of the BBB, the capillaries of the choroid plexus are fenestrated, and holo-transferrin can readily cross endothelial cells to reach the basolateral membrane of the polarized choroidal epithelium. Iron binds to transferrin synthesized or transported into the interstitial fluid or cerebrospinal fluid (CSF) in the ventricles. Apo-transferrin (iron-free transferrin) and holo-transferrin probably return to the systemic circulation by passing through the arachnoid villi into veins that return blood to the systemic circulation (Moos et al., 2007; Rouault, 2013).

As a result of aging, iron accumulates as ferritin in the microglia, astrocytes, and oligodendrocytes. It is concentrated in the globus pallidus, substantia nigra, putamen, caudate nucleus, dentate nucleus, and frontal cortex areas. Impaired regulation of iron homeostasis may lead to excessive accumulation of free cytosolic iron. Free cytosolic Fe II reacts with endogenously generated hydrogen peroxide to yield hydroxyl radicals, damaging cell membranes (Benarroch, 2009).

Iron Deficiency: Prevalence and Implications in Migraine

The recommended daily iron intake is 18 mg/day for women aged 20 to 50 (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015). There is no prevalence study on iron deficiency in migraine, but studies found higher iron deficiency anemia (IDA) in migraine patients when compared with the control group (Pamuk et al., 2016; Selen and Ruhan, 2016; Tayyebi et al., 2019; Meng et al., 2021; Sari and Kama Başci, 2024). Dietary iron intake was inversely associated with severe headache or migraine in women aged 20-50 years. The serum ferritin was negatively associated with migraine. There was no significant relationship between dietary iron and serum ferritin and severe headache or migraine in men (Tayyebi et al., 2019). The case-control study comparisons revealed a

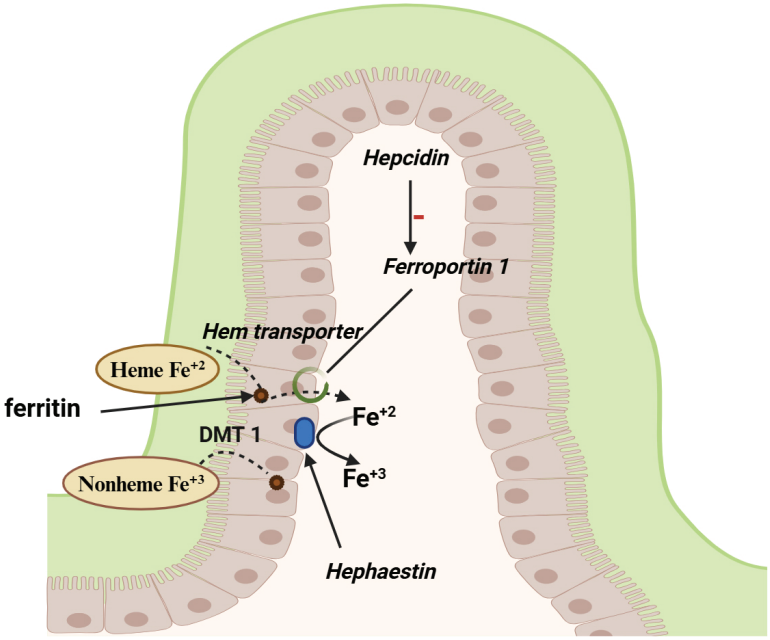

Fig. 1. Absorption of heme and non-heme iron in the intestinal tract, especially the duodenum. DMT 1: Divalent Metal Transporter 1.

significant difference in IDA but not hemoglobin and serum ferritin levels in female migraine patients. This might suggest iron supplements are an effective treatment or prevention in patients with migraine associated with IDA (Selen and Ruhan, 2016). Also, in a study, the relationship between IDA and migraine was more significant among girls and women, as the relative prevalence of IDA in girls suffering from migraine was higher than that of men and boys. Moreover, there was a significant relationship between migraine and hemoglobin levels (Sari and Kama Başci, 2024). Another study also found a higher prevalence of migraine in patients with iron deficiency but did not find a relation between migraine severity and anemia, only menstruation-related migraine. An inverse relationship was found between VAS, HIT-6, and ferritin levels (Pamuk et al., 2016). In general, there is a relationship between migraine and iron, and there is more information in the literature that it is not correlated with pain intensity and frequency. However, the relationship needs to be clarified with double-blind, randomized studies.

The neurological impact: How iron affects migraine symptoms

Studies have revealed that iron is a crucial player in the synthesis of key neurotransmitters such as serotonin, dopamine, and norepinephrine. Iron acts as a cofactor for tyrosine hydroxylase and tryptophan hydroxylase, which are responsible for the synthesis of dopamine and serotonin. Serotonin, a multifunctional neurotransmitter that regulates sleep, appetite, and memory, is particularly affected by iron levels. During a migraine attack, the level of serotonin in the CNS decreases, leading to the dilation of blood vessels and the release of inflammatory substances. This cascade of events triggers pain signals, leading to headaches and associated symptoms (Deen et al., 2017).

Migraine patients present chronic dopaminergic hypofunction. This dopaminergic dysfunction leads to overexpression of dopamine receptors, resulting in increased sensitivity to dopaminergic stimulation and reduced inhibitory control in the trigeminal neurons. Lower dopamine concentrations suggest inducing some of the prodromal symptoms, such as yawning or drowsiness, and then subsequently, during migraine attacks, dopamine levels increase, presenting as nausea or hypotension. Dopamine, mainly D2, plays an important part in the modulation of nociception. Additionally, recent findings indicate changes in the expression of three genes involved in nigrostriatal dopamine malfunction due to IDA (Jellen et al., 2013; Burstein et al., 2015).

Estrogen contributes to regulating iron metabolism; however, the potential effects of estrogen on iron metabolism are not clearly understood. A study found that estrogen modulates ferroportin expression at the mRNA level. Estrogen (17β-estradiol) could significantly inhibit the mRNA transcription of ferroportin. Cells with ferroportin deficiency were resistant to estrogen-induced iron alterations through ferroportin. Consistent with the *in vitro* findings, ferroportin expression was elevated upon estrogen deficiency in mice with ovariectomy. These results suggest that estrogen plays a crucial role in iron metabolism by

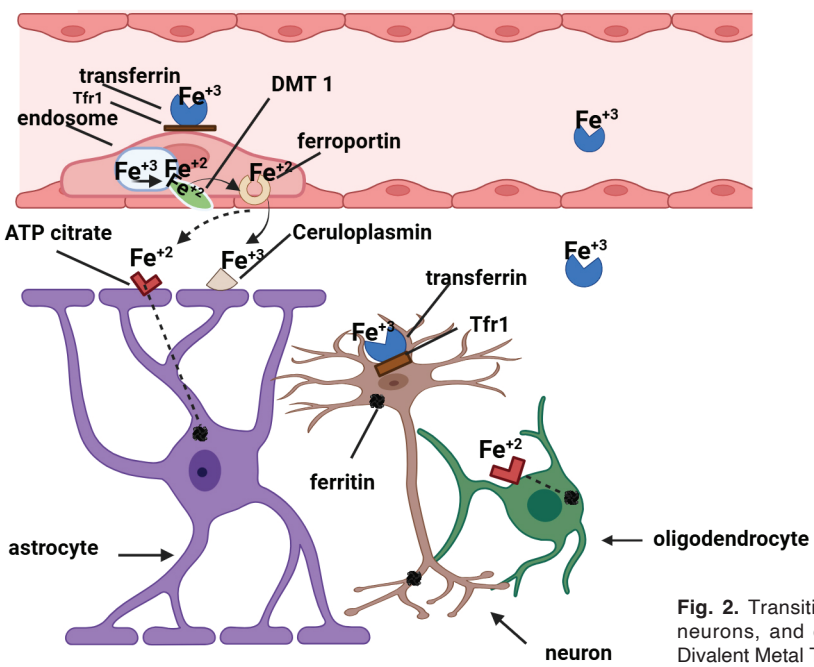

Fig. 2. Transition of iron across the blood-brain barrier into astrocytes, neurons, and oligodendrocytes. Tfr1: Transferrin receptor 1, DMT 1: Divalent Metal Transporter 1.

repressing ferroportin expression (Qian et al., 2015).

Iron is necessary for monoamine oxidase enzyme (MAO) synthesis and decreasing MAO simultaneously in IDA and migraine, and its increase after iron supplementation suggests the effect of the iron regimen on the severity and prevalence of migraine attacks in both IDA and non-IDA groups (Patiroglu and Dogan, 1991).

Gender differences: Understanding the influence of iron on migraine across genders

The gender disparity in migraine is believed to be partly mediated through fluctuations in ovarian steroid hormones, especially estrogen and progesterone. However, the exact mechanisms are not yet completely understood. Estrogen is considered the primary female sex steroid, and elevated concentrations of E2 have been positively correlated with iron demand and the release of iron into the systemic circulation and negatively correlated with hepcidin concentration (Hamad et al., 2020). However, the exact mechanism by which E2 influences iron regulation remains to be determined. *In vitro* studies and rodent models suggest that E2 may support the upregulation of genes involved in iron metabolism (Stuckey et al., 2006; Yang et al., 2012; Bajbouj et al., 2018; Hamad et al., 2020). *In vivo* studies have demonstrated a marked suppression in serum hepcidin levels in females treated with large doses of E2 during *in vitro* fertilization (Lehtihet et al., 2016). Low serotonin (5-HT) levels and reduced brain serotonin synthesis have also been linked to migraine. 5-HT is synthesized from tryptophan, transforming into 5-hydroxytryptophan (5-HTP) via the enzyme tryptophan hydroxylase (TPH). Estrogen can influence enzymes at different stages of tryptophan metabolism. A study explored the interrelations between serotonin, cortical excitability, and sex hormones in female and male rats. Their findings showed elevated estrogen levels increase cortical excitability, while estrogen withdrawal decreases Cortical Spreading Depression (CSD) and normalizes it, and 5-HTP decreases the occurrence of CSD, but only in the presence of ovarian hormones. In oophorectomized rats that received estradiol replacement, increased CSD was observed, which decreased after estradiol withdrawal (Chauvel et al., 2018). Another study utilized a multibehavioral model of migraine in rats and investigated responses to estrogen exposure. Compared with vehicle treatment, estradiol treatment led to a statistically significant decrease in locomotor activity, significant light and noise avoidance, allodynia-associated behaviors, and an enhanced acoustic startle. Moreover, estradiol treatment increased the expression of estrogen receptor genes, inflammation, vasodilation, and endogenous cannabinoid metabolism. Also, this treatment activated nociception-related ERK (extracellular signal-regulated kinase) (Chauvel et al., 2018). In this study, nitroglycerin injections were administered to provoke migraine headaches in rats for the effect of estrogen on the expression of nociceptive signal proteins such as brain-derived neurotrophic factor (BDNF), tropomyosin receptor kinases (TrkB), as well as ERK and its downstream target, cAMP-responsive element binding protein (CREB). A positive relationship was observed between the BDNF/TrkB and ERK/CREB pathways and the contribution of estrogen. Indeed, female ovariectomized rats showed a significant decrease in BDNF, TrkB, p-CREB, and p-ERK expression in migraine attacks and intervals compared with rats with intact ovaries. However, the administration of estrogen recovered the expression in these ovariectomized rats. Moreover, researchers observed higher serum BDNF levels in female than in male rats during migraine attacks (Guo et al., 2017). Another study determined the effect of 17β-estradiol on the expression and activity of genes involved in neurogenic inflammation in females with pure menstrual migraine and age- and sex-matched healthy individuals. Cultured peripheral blood mononuclear cells from these participants were treated with 17β-estradiol at physiological and pharmacological doses. The pharmacological dose caused a significant increase in mRNA expression of CGRP in both groups. In contrast, the physiological dose caused a significant decrease in mRNA expression of CRP, CGRP, IL-1β, NO, and iNOS activity only in females with pure menstrual migraine (Karkhaneh et al., 2015).

Testosterone has consistently been shown to suppress hepcidin in both males and females potently. Rodent models demonstrated that testosterone-dependent upregulation of epidermal growth factor receptors in the liver causes hepcidin downregulation. In both young (19-35 years) and older (59-75 years) males, testosterone suppresses hepcidin in a dose-dependent manner; these changes are strongly correlated with increases in hemoglobin and hematocrit (Bachman et al., 2010; Latour et al., 2014)

Iron supplements: Efficacy and considerations in migraine treatment

This topic requires further experimental investigation. Most women aged 20-50 consumed less iron than their recommended dietary allowances. Dietary iron intake was inversely associated with severe headaches or migraine in women aged 20-50. Similarly, in women over 50, serum ferritin was also negatively associated with severe headache or migraine. There was no significant relationship between dietary iron and serum ferritin and severe headache or migraine in men (Meng et al., 2021).

Neuroinflammation and oxidative stress: Interplay with iron in migraine pathophysiology

Neuroinflammation is thought to play a significant role in the development and progression of migraine.

During a migraine attack, there is often an increase in inflammatory markers in the brain. Inflammatory processes can affect brain cells and alter pain pathways, potentially exacerbating migraine symptoms. Some studies suggest that chronic migraines may involve ongoing neuroinflammation, which could contribute to the persistence and severity of the condition. The trigemino-vascular system is the key component in migraine headaches. The dysfunction of the trigeminovascular system and energy metabolism can lead to migraine. The primary afferent nerve of the trigeminal nerve innervates the pia mater and dural meningeal vessels. Its efferent projection fibers connect with secondary neurons in the trigeminal nucleus caudalis (TNC) of the brainstem. The nerve fibers of TNC project to the thalamus and then rise further to communicate with the higher cortical area. Cortical spreading depression can trigger neurogenic meningeal inflammation and activate the trigemino-vascular system (Kursun et al., 2021). Stimulation of the trigeminal nerve causes the release of neuropeptides, including CGRP, SP, NO, VIP, and 5-HT, leading to neurogenic inflammation by the increased vascular permeability, leukocyte infiltration, glial cell activation, and increased production of inflammatory mediators, such as cytokines and chemokines. Vasoactive peptides, such as CGRP and SP, bind their receptors on the smooth muscle of dural vessels and cause vasodilation. The release of neuropeptides causes mast cell degranulation, which leads to the release of histamine and serotonin and selectively can cause the release of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, and all of them lead to endothelium-dependent vasodilation. The binding of the released SP to the NK1 receptors expressed in the microvascular blood vessels disrupts the membrane and causes plasma protein leakage and leukocyte extravasation. Mast cells are closely associated with neurons, especially in the dura, where they can be activated following trigeminal nerve and cervical or sphenopalatine ganglion stimulation. However, microglia activation leads to the production of inflammatory mediators and cytotoxic mediators. The production of reactive oxygen species can lead to the opening of the mitochondrial permeability transition pore (mPTP), which can increase the markers of oxidative stress, and closing can lead to a decrease in antioxidants (Zhang et al., 2010). If neuroinflammation is uncontrolled, it might contribute to neurodegeneration, iron accumulation, and the progression of related diseases.

Abnormal mitochondrial function can result in high intracellular Ca^{2+} levels, excessive production of free radicals, and deficient oxidative phosphorylation, which ultimately causes energy failure in neurons and astrocytes, which have been hypothesized to play a role in migraine pathophysiology. Therefore, iron may be a determinant of chronicity. When energy metabolism is abnormal, the following abnormalities will occur in mitochondria in migraine mPTP and IMAC are pathologically open, releasing cytochrome C and reactive oxygen species, and calcium ions inflow through the MCU channel, resulting in calcium overload in the mitochondria, the dysfunction of the mitochondrial respiratory chain leads to reactive oxygen species and insufficient production of ATP, which will stimulate nitric oxide production. The decrease in NAD+/NADH can change SIRT3 and CYPD, decrease mitochondrial membrane potential, and open mPTPs. An abnormal proportion of pro-apoptotic and anti-apoptotic proteins can lead to apoptosis and migraine (Wang et al., 2023).

Besides the excessive reactive oxygen species induced by iron deposition, there is another pathway causing neuroinflammation via NLRP3 inflammasome activation in response to free cellular iron (Xu et al., 2023). Fe^{2+}-specific chelators can rescue peripheral blood mononuclear cells from an LPS stimulation-induced Fe^{2+} increase following Fe^{2+} dose-dependent IL-1β production, which results from NLRP3 inflammasome activation (Nakamura et al., 2016; Huang et al., 2023). Thus, iron may also be involved in migraine-related neuroinflammation induced by NLRP3 inflammasome activation (Fig. 3).

Ongoing studies aim to better understand how regulating iron levels might influence neuro-inflammation and migraine. Notably, some research is exploring whether iron supplements or chelators (which help remove excess iron) might impact migraine frequency or intensity.

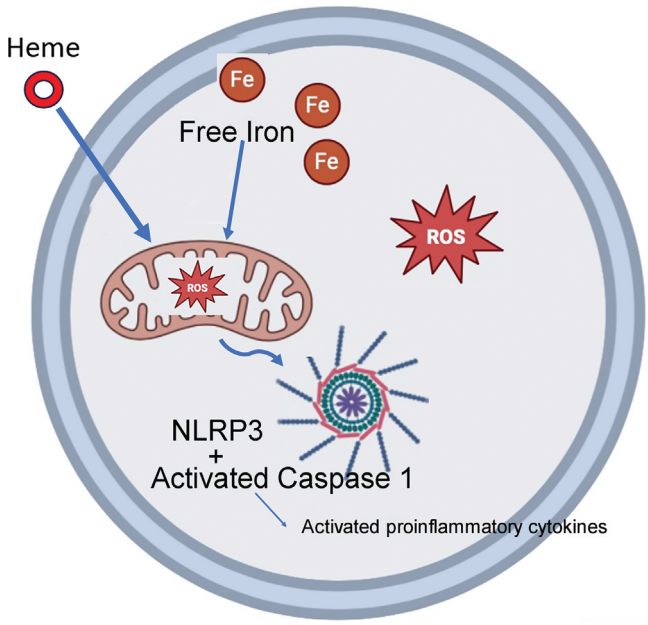

Fig. 3. Iron, NLRP3, and migraine-related neuroinflammation are interconnected through various mechanisms. Extracellular heme or free cytosolic iron can activate the NLRP3 inflammasome, potentially via reactive oxygen species (ROS) generated from mitochondria or phospholipid membranes. The formation of the NLRP3 inflammasome complex and subsequent activation of caspase-1 result in the release of pro-inflammatory cytokines, contributing to neuroinflammation.

Imaging techniques: Insights into iron accumulation in the migraine brain

The structures richest in iron are the globus pallidus and substantia nigra, followed by the red nucleus, putamen, caudate nucleus, dentate nucleus, and subthalamic nucleus (Welch et al., 2001; Dominguez et al., 2019; Chen et al., 2021, 2022; Xu et al., 2023; Li et al., 2024). The periaqueductal gray (PAG) is involved in the descending brainstem modulating systems; therefore, dysfunction of this area could lead to the progression of migraine. The mechanism by which iron deposits increase in the PAG of Chronic Migraine (CM) patients is still unknown.

Meanwhile, patients with CM had a significantly higher volume of iron deposits than Episodic Migraine (EM) in multiple subcortical nuclei, especially in the nucleus accumbens (NAC). The volume of iron in the NAC can be used to distinguish patients with CM from EM with a sensitivity of 85.45% and specificity of 71.53% as the most valuable neuroimaging marker in all subcortical nuclei; higher iron deposition in the NAC was significantly associated with disease progression and higher HIT-6, MIDAS, and PSQI. The prevailing literature generally indicates that repeated migraine attacks are associated with increased iron accumulation in multiple deep nuclei that are involved in central pain processing and migraine pathophysiology. It remains unclear whether iron accumulation in the antinociceptive network has a causative role in developing CM headaches (Xu et al., 2023).

PAG is activated during migraine attacks, and the activation of PAG may contribute to hyperemia in parallel to the increase in free radicals, which in turn may contribute to an increase in iron. It is suggested that the high concentration of transferrin receptors may contribute to high iron levels in the PAG (Welch et al., 2001). Accumulating cellular iron was found to differ in CM and EM patients and was associated with the duration of pain. In a recent study, patients with CM showed increased iron deposition in the red nucleus and PAG compared with patients with EM and controls. The iron accumulation volume in the PAG was correctly identified in patients with CM and was associated with elevated endothelial dysfunction and BBB disruption biomarkers. They showed a correlation between levels of sTWEAK (soluble tumor necrosis factor-like weak inducer of apoptosis). These findings suggest that mechanisms implicated in the pathophysiology of migraine other than inflammation, such as endothelial dysfunction and BBB disruption, might play a role in iron deposition. sTWEAK levels are surrogate markers of endothelial dysfunction and atherosclerosis. The main effects of sTWEAK interactions are inflammation and cell death or cell proliferation, depending on the particular cell type and cytokine context. High sTWEAK levels can contribute to the blood-CSF barrier and BBB permeabilization, which may contribute to the inflammatory cascade in the CNS and iron accumulation. Iron deposits in the globus pallidus and PAG have been associated with the frequency of migraine attacks and the time of evolution of migraine, suggesting a causal relation between recurring attacks and the accumulation of iron (Dominguez et al., 2019).

A multi-echo gradient echo MR sequence was used to obtain raw quantitative susceptibility mapping (QSM) data from CM patients. CM presented a higher susceptibility value over the whole cerebral gray matter. There was no correlation between susceptibility values and clinical variables. The ROC analysis showed that QSM had high diagnostic efficacy in discrimination. The causes of increased iron deposition in brain gray matter in CM could include the transferrin present in the brain and its receptors, which may contribute to iron transfer to cells. Transferrin is much more distributed in the brain's gray matter than in the white matter. Therefore, the increased iron deposition might be associated with higher iron metabolism. The free radicals could easily damage the neurons with high iron transferrin levels, and the migraine attacks could lead to hyperoxia episodes and then increase the iron-induced free radical cell damage, leading to increased iron deposition. Synaptic plasticity and increased neuronal excitability may contribute to this process. The studies demonstrated a correlation between clinical variables and iron deposition when focusing on the gray nuclei area (Chen et al., 2021; Meng et al., 2021). Increased cerebral iron deposition was present in CM patients compared with healthy controls, and a positive correlation was identified between susceptibility value and VAS score (Chen et al., 2021).

EM patients presented an increased susceptibility value in the left putamen and bilateral substantia nigra (SN) compared with healthy controls. There was no correlation between susceptibility value and clinical variables (Dominguez et al., 2019). Iron deposition could be considered an independent factor in the occurrence of migraines, warranting further research.

Clinical implications: Translating iron-migraine research into practice

Iron accumulation in the PAG and red nucleus of CM patients was higher than in EM patients. This accumulation can be due to recurrent attacks with secondary damage since endothelial dysfunction and BBB disruption biomarkers are also elevated in this group. This could lead to progressive dysfunction and chronification (Dominguez et al., 2019). Dietary iron intake has different effects on migraine in women of various ages, and these different effects may be due to age-related menstrual changes. Women aged between 20 and 50 should have a higher awareness of the recommended dietary allowance and increase their dietary iron intake if needed, which may play an important role in preventing severe headaches or migraine (Meng et al., 2021). Higher serum ferritin levels in women aged 50 and above may protect against

migraine. Dopamine plays a role in the pathogenesis of migraine, and iron is an essential trace element for the synthesis of dopamine. Studies suggest that iron deficiency could lead to dopaminergic neurodegeneration (Matak et al., 2016). The regulation of dopamine by iron may be a potential mechanism for the beneficial effect of iron on migraine.

As a result, iron deficiency and low ferritin levels should be considered when planning a migraine patient's initial treatment, and any deficiencies should be replaced. Informing the patient about daily iron intake in their diet will also contribute to preventing migraine attacks from becoming chronic, reducing their frequency and the severity of attacks, especially in menstrual migraine.

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References

Bachman E., Feng R., Travison T., Li M., Olbina G., Ostland V., Ulloor J., Zhang A., Basaria S., Ganz T., Westerman M. and Bhasin S. (2010). Testosterone suppresses hepcidin in men: A potential mechanism for testosterone-induced erythrocytosis. J. Clin. Endocrinol. Metab. 95, 4743-4747.

Bajbouj K., Shafarin J., Allam H., Madkour M., Awadallah S., El-Serafy A., Sandeep D. and Hamad M. (2018). Elevated estrogen levels suppress hepcidin synthesis and enhance serum iron availability in premenopausal women. Exp. Clin. Endocrinol. Diabetes 126, 453-459.

Benarroch E. (2009). Brain iron homeostasis and neurodegenerative disease. Neurology 72, 1436-1440.

Burstein R., Noseda R. and Borsoo K.D. (2015). Migraine: Multiple processes, complex pathophysiology. J. Neurosci. 35, 6619-6629.

Chauvel V., Multon S. and Schoenen J. (2018). Estrogen-dependent effects of 5-hydroxytryptophan on cortical spreading depression in rat: Modeling the serotonin-ovarian hormone interaction in migraine aura. Cephalalgia 38, 427-436.

Chen Z., Dai W., Chen X., Liu M., Ma L. and Yu S. (2021). Voxel-based quantitative susceptibility mapping revealed increased cerebral iron over the whole brain in chronic migraine. Mol. Pain 17, 17448069211020894.

Chen Z., Zhao H., Chen X., Liu M., Li X., Ma L. and Yu S. (2022). The increased iron deposition of the gray matter over the whole brain in chronic migraine: An exploratory quantitative susceptibility mapping study. Mol. Pain 18, 17448069221074987.

Chifman J., Laubenbacher R. and Torti S.V. (2014). A systems biology approach to iron metabolism. Adv. Exp. Med. Biol. 844, 201-225.

Deen M., Christensen C.E., Hougaard A., Hansen H.D., Knudsen G.M. and Ashina M. (2017). Serotonergic mechanisms in the migraine brain - a systematic review. Cephalalgia 37, 251-264.

Domínguez C., López A., Ramos-Cabrer P., Vieites-Prado A., Pérez-Mato M., Villalba C., Sobrino T., Rodriguez-Osorio X., Campos F., Castillo J. and Leira R. (2019). Iron deposition in periaqueductal gray matter as a potential biomarker for chronic migraine. Neurology 92, e1076-e1085.

Guo J.Q., Deng H.H., Bo X. and Yang X.S. (2017). Involvement of BDNF/TrkB and ERK/CREB axes in nitroglycerin-induced rat migraine and effects of estrogen on these signals in the migraine. Biol. Open 6, 8-16.

Hamad M., Bajbouj K. and Taneera J. (2020). The case for an estrogen-iron axis in health and disease. Exp. Clin. Endocrinol. Diabetes 128, 270-277.

Huang W., Zhang Z., Qiu Y., Gao Y., Fan Y., Wang Q. and Zhou Q. (2023). NLRP3 inflammasome activation in response to metals. Front. Immunol. 14, 1055788.

Jellen L.C., Lu L., Wang X., Unger E.L., Earley C.J., Allen R.P., Williams R.W. and Jones B.C. (2013). Iron deficiency alters the expression of dopamine-related genes in the ventral midbrain in mice. Neuroscience 252, 13-23.

Karkhaneh A., Ansari M., Emamgholipour S. and Rafiee M.H. (2015). The effect of 17β-estradiol on gene expression of calcitonin gene-related peptide and some pro-inflammatory mediators in peripheral blood mononuclear cells from patients with pure menstrual migraine. Iran J. Basic Med. Sci. 18; 894-901.

Kursun O., Yemisci M., van den Maagdenberg A.M.J.M. and Karatas H. (2021). Migraine and neuroinflammation: The inflammasome perspective. J. Headache Pain 22, 55.

Latour C., Kautz L., Besson-Fournier C., Island M.L., Canonne-Hergaux F., Loréal O., Ganz T., Coppin H. and Roth M.P. (2014). Testosterone perturbs systemic iron balance by activating epidermal growth factor receptor signaling in the liver and repression of hepcidin. Hepatology 59, 683-694.

Lehtihet M., Bonde Y., Beckman L., Berinder K., Hoybye C., Rudling M., Sloan J.H., Konrad R.J. and Angelin B. (2016). Circulating Hepcidin-25 is reduced by endogenous estrogen in humans. PLoS One 11, e0148802.

Li X., Zhao H., Liu M. and Chen Z. (2024). Increased brain iron deposition in episodic migraine: A pilot voxel-based quantitative susceptibility mapping. Curr. Med. Imaging 20, e260423216207.

Matak P., Matak A., Moustafa S., Aryal D.K., Benner E.J., Wetsel W. and Andrews N.C. (2016). Disrupted iron homeostasis causes dopaminergic neurodegeneration in mice. Proc. Natl. Acad. Sci. USA 113, 3428-435.

Meng S.H., Zhou H.B., Li X., Wang M.X., Kang L.X., Fu J.M., Li X., Li X.T. and Zhao Y.S. (2021). Association between dietary iron intake and serum ferritin and severe headache or migraine. Front. Nutr. 8, 685564.

Moos T., Rosengren Nielsen T., Skjørringe T and Morgan E.H. (2007). Iron trafficking inside the brain. J. Neurochem. 103, 1730-1740.

Nakamura K., Kawakami T., Yamamoto N., Tomizawa M., Fujiwara T., Ishii T., Harigae H. and Ogasawara K. (2016). Activation of the NLRP3 inflammasome by cellular labile iron. Exp. Hematol. 44, 116-124.

Pamuk G.E., Top M.Ş., Uyanık M.Ş., Köker H., Akker M., Ak R., Yürekli Ö.A. and Çelik Y. (2016). Is iron-deficiency anemia associated with migraine? Is there a role for anxiety and depression? Wien. Klin. Wochenschr. 128, 576-580.

Patiroglu T. and Dogan P. (1991). Iron deficiency anemia and catecholamine metabolism. Indian Pediatr. 28, 51-56.

Qian Y., Yin C., Chen Y., Zhang S., Jiang L., Wang F., Zhao M. and Liu S. (2015). Estrogen contributes to regulating iron metabolism by governing ferroportin signaling via an estrogen response element. Cell Signal 27, 934-942.

Rouault T.A. (2013). Iron metabolism in the CNS: implications for neurodegenerative diseases. Nat. Rev. Neurosci. 14, 551-64.

Rouault T.A. and Cooperman S. (2006). Brain iron metabolism. Semin. Pediatr. Neurol. 13, 142-148.

Sari U.S. and Kama Başci Ö. (2024). Association between anemia severity and migraine in iron deficiency anemia. Eur. Rev. Med. Pharmacol. Sci. 28, 995-1001.

Selen G.Ö. and Ruhan K.Ö. (2016). Iron deficiency anemia is associated with menstrual migraine: A case-control study. Pain Med. 17, 596-605.

Stuckey R., Aldridge T., Lim F.L., Moore D.J., Tinwell H., Doherty N., Davies R., Smith A.G., Kimber I., Ashby J., Orphanides G. and Moggs J.G. (2006). Induction of iron homeostasis genes during estrogen-induced uterine growth and differentiation. Mol. Cell. Endocrinol. 253, 22-29.

Tayyebi A., Poursadeghfard M., Nazeri M. and Pousadeghfard T. (2019). Is there any correlation between migraine attacks and iron deficiency anemia? A case-control study. Int. J. Hematol. Oncol. Stem Cell Res. 13, 164-171.

U.S. Department of Health and Human Services and U.S. Department of Agriculture (2015). 2015-2020 Dietary Guidelines for Americans. 8th ed.

Wang Y., Wang Y., Yue G and Zhao Y. (2023). Energy metabolism disturbance in migraine: From a mitochondrial point of view. Front. Physiol. 14, 1133528.

Welch K.M , Nagesh V.,Aurora S.K. and Gelman N. (2001). Periaqueductal gray matter dysfunction in migraine: Cause or the burden of illness? Headache 41, 629-637.

Xu X., Zhou M., Wu X., Zhao F., Luo X., Li K., Zeng Q., He J., Cheng H., Guan X., Huang P., Zhang M. and Liu K. (2023). Increased iron deposition in nucleus accumbens associated with disease progression and chronicity in migraine. BMC Med. 21, 136.

Yang Q., Jian J., Katz S., Abramson S.B. and Huang X. (2012). 17β-Estradiol inhibits iron hormone hepcidin through an estrogen-responsive element half-site. Endocrinology 153, 3170-3178.

Zhang X., Levy D., Noseda R., Kainz V., Jakubowski M., Burstein R., Kainz V., Jakubowski M. and Burstein R. (2010). Activation of meningeal nociceptors by cortical spreading depression: Implications for migraine with aura. J. Neurosci. 30, 8807-8814.

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