The connection between migraine and the microbiome

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Foreword

This research was motivated by a personal interest in both migraine research and the microbiome. The aim of this study is to deepen the understanding of the intricate connections between these two fields, possibly discovering new approaches to combat migraine prevalence. Special thanks are extended to Alexander Kurilshikov for his invaluable supervision and guidance throughout this thesis.

Abstract

This study explores the intricate relationship between the human microbiota and migraine, focusing on recent research that elucidates both direct and indirect mechanisms linking gut microbial composition to migraine pathophysiology. Recent studies highlight the microbiome's influence on immune modulation, inflammation, and metabolic pathways, which are implicated in migraine onset and severity. The role of specific microbial taxa and microbiome composition in migraine pathogenesis is examined. Key findings indicate that the gut microbiota may influence migraine through inflammatory pathways, immune modulation, and metabolic effects. Insights from this research underscore the microbiome's significant role in neurological health and pave the way for future investigations into microbiota-based treatments for migraine management.

Introduction

Migraine is a neurological disorder significantly impairing quality of life for more than one billion individuals (Amiri et al., 2022). Migraine symptoms include throbbing head pain, nausea and sensitivity to movement, which can result in the loss of sleep and in some cases even suicide (Amiri et al., 2022; Puledda et al., 2023; Goadsby et al., 2017). While migraine is one of the biggest contributors to the global burden of neurological conditions, the physiological mechanisms that precede the attacks are not completely known. Research has found a wide range of possible factors affecting migraine onset, ranging from the immune system to neurotransmitters such as serotonin (Biscetti et al., 2021; Hamel & Currents, 2007).

Ongoing research has suggested a relationship between the gut microbiome and the onset of migraines, indicating a bidirectional communication pathway between the brain and the gut (Hindiyeh & Aurora, 2015; He et al., 2023.). The interaction between the microbiota and the brain, known as the gut-brain axis, involves extensive interactions through multiple possible factors. These interactions are influenced by gut inflammation and the composition of microbiota, all possibly contributing to migraine onset. The microbiome has already been found to play an important role in several bodily functions, such as immune modulation, metabolism and overall health (Amon & Sanderson, 2017; Beloborodova & Grechko, 2021). Dysbiosis of the microbiome has already been linked to several neurological disorders, highlighting the possibility of its impact on migraines (Beloborodova & Grechko, 2021).

This literature review looks into the complex interplay between the microbiome and migraines, investigating how the microbiome might influence migraine onset through mechanisms like inflammation, immune modulation, and metabolic pathways. Potential connections are explored, as well as more direct established connections. Understanding and revealing more of these connections could pave the way for novel therapeutic approaches, offering hope for improved management and treatment of migraines. The research question that is explored in this review is: How does the microbiome influence the pathogenesis of migraine?

Physiology of migraine

Migraine is a complex neurological disorder which affects the quality of life to a significant degree, particularly during peak productive years (Puledda et al., 2023; Goadsby et al., 2017). A clear characteristic for migraine is unilateral, throbbing head pain that is sensitive to movement and various sensory inputs, including visual and auditory stimuli. The premonitory phase can begin up to 48 hours before the headache, with symptoms such as irritability, tiredness, reduced concentration, and yawning. Following most migraine attacks is the postdrome phase, characterized by prolonged feelings of tiredness and feeling sick for up to a day. Alongside this, an estimated one-third of migraine patients experience neurological symptoms, including cortical disturbances which are collectively known as migraine aura (Goadsby et al., 2017).

Recent study found the burden of neurological conditions to be much heavier than expected in the past (Steinmetz et al., 2024; Sisodiya et al., 2024) . In 2021, 443 million years of healthy life were lost due to neurological conditions, caused by premature death, illness and disability. This causes neurological conditions to contribute the most to the global disease burden, ranking even above cardiovascular diseases (Steinmetz et al., 2024; Sisodiya et al., 2024). Migraine was one of the biggest contributors these conditions, highlighting the importance of recognizing it as a priority for research.

The physiological mechanisms behind migraine are still not completely known, causing the origin of migraine to be under debate as of today. Migraine onset is believed to be influenced by mechanisms in both the central and peripheral trigeminovascular system (Della Pietra et al., 2024; Puledda et al., 2023).

More direct causes of migraine have been investigated for a long time and studies have found several factors that could be of influence in migraine pathogenesis. A study by Della Pietra et al. (2024) explored the role of mechanosensitive mechanisms in migraine symptoms. The paper argued that during migraine attacks, there is heightened interaction among trigeminal ganglia neurons, glial cells, meningeal immune cells, and local vessels. Mechanical forces arising from dilated vessels and pulsations can via other mechanisms lead to pain by neuronal sensitization and inflammation. The researchers highlighted the importance of giving more attention to said mechanisms in migraine pathology, giving the evidence provided in the paper. A different study found ATP-sensitive potassium channels to be a common factor in migraine, despite the effects of external factors such as the environment, diet and sleep (Al-Karagholi et al., 2021).

An article by Ashina et al. (2019) reviewed four decades of research on the trigeminovascular system’s role in migraines. Their study found trigeminal nerve activation, vasodilation and inflammation and neuropeptides to have an influence on migraine. The underlying mechanisms of these factors include neurogenic inflammation, inflammatory mediators and calcitonin gene-related peptide to be a potential cause of migraine symptoms.

Causes for migraine	Key aspects
Trigeminovascular system - central - peripheral	- **Mechanisms**; Trigeminal nerve activation, vasodilation and inflammation, neuropeptides - **Causes for migraine symptoms**; Neurogenic inflammation, inflammatory mediators, calcitonin gene-related peptide
Mechanosensitive Mechanisms	- **Mechanisms**; Heightened interaction between trigeminal ganglia neurons, glial cells, meningeal immune cells, local vessels - **Causes for migraine symptoms**; Dilated vessels, pulsations
ATP-Sensitive Potassium Channels	- Common factor in migraine

Table 1: *possible causes for migraine found from research, highlighting different mechanisms through which they occur and the actual causations of migraine symptoms*

The previous lines of research highlight the diversity of mechanisms possibly influencing the onset of migraine attacks and the complexity of which. Looking at it from different perspectives is of importance to fully understand it. The central nervous system seems to be of importance when looking at migraine onset, but also factors such as the immune system and metabolism seem to play a role.

Recent research has highlighted the possible relationship between the microbiome and migraines. The paper by Hindiyeh & Aurora (2015) discussed the ongoing research on the connection of the microbiome and migraines and found there to be an established connection between the two. It was known for the brain to influence the gut, but the connection is really bi-directional. Inflammation in the GI tract could have an effect on the stimulatory role of the trigeminovascular system on migraine onset. Research has also found the gut microbiota to be a factor influencing the brain-gut axis, potentially affecting migraine through this pathway as well (Hindiyeh & Aurora, 2015). Distinct bacterial taxa and the overall composition of the gut microbiota is possibly a causal influence on migraine pathology (He et al., 2023). The well-known role that the microbiome plays in a wide array of diseases and its influence on the central nervous system makes it a factor in migraine onset worth investigating.

The microbiome: an overview

The human microbiome consists of numerous different communities of bacteria (plus fungi and viruses), which amount to trillions of microorganisms, all together reaching a complexity greater than the human genome itself (Amon & Sanderson, 2017; Beloborodova & Grechko, 2021). The microbiome of every human is unique and is tailored to your body from your birth onwards. Having commensal bacteria present in the gut is of great importance in order to harbor your immune system, the processing of nutrients and other characteristics of the body in general (Valles-Colomer et al., 2019).

Certain gut microorganisms, termed 'autochthonous,' are considered native to their host due to their long-term co-adaptation. This suggests that the gut microbiota is not just a random assortment of organisms introduced via food but a specialized community that has evolved to thrive within a specific host environment (Flint, H. J., 2020). While new organisms continually enter the gut, most are 'allochthonous' or transient, passing through without establishing significant populations (Flint, H. J., 2020).

The epithelial-immune-gut barrier plays a crucial role in maintaining homeostasis in the host body, with the gut microbiota often referred to as a significant, though "invisible," organ. The gut microbiota's function is vital for the host organism's health. Severe gut dysbiosis can increase the risk of various diseases, including those affecting the brain, highlighting the interconnectedness between gut health and overall well-being, including neurological conditions (Beloborodova & Grechko, 2021).

A lot of research has been conducted on the topic of the microbiota in general, but also on the effects that it has on the body and its variety of systems. The more research that is conducted, the more it seems like the microbiome has an effect on a wide array of bodily functions, ranging from the immune system to your mental wellbeing.

Research by Laterza, L. (2022) investigated the changes in gut microbiota after surgery. Results showed that despite the large difference between individual's microbial composition, the gut microbiota of patients that experienced infections exhibited a relative predominance of potentially pathogenic species in their gut microbiota. This highlights the previously mentioned interconnectedness between the microbiome and health and disease.

A study by Sanna et al. (2019) found that increased gut production of butyrate, driven by host genetics, was associated with improved insulin response. Butyrate is a type of short-chain fatty acid (SCFA). Deviations in the production of propionate, another SCFA produced in the gut, were found to be casually related to a higher risk of developing type 2 diabetes. This study shows the microbiome's ability to affect diseases through different factors.

Studies have also shown the microbiome to affect diseases connected to the central nervous system. Foster and Neufeld (2013) explored the connection between the microbiome and anxiety and depression, focusing on the gut-brain axis and the effectiveness of probiotics. The study found that germ-free mice, which lack microbiota, exhibit an exaggerated stress response, linking microbiota to hypothalamic-pituitary-adrenal axis reactivity. Gut microbiota also influences hypothalamic-pituitary-adrenal axis development and stress reactivity throughout life. The study also found that germ-free mice show reduced anxiety-like behavior but elevated corticosterone levels, which normalize with early-life reintroduction of microbiota. Behavior changes correspond to microbiota alterations, emphasizing the microbiota's role in stress-related behaviors and thus the CNS. The paper also noted the findings of emerging studies that changes in the gut bacteria affect the CNS via the serotonergic, GABAergic and plasticity related signaling systems. Supporting these findings, a study by Valles-Colomer et al. (2019) found connections between certain strains of bacteria to be associated with higher quality of life indicators, as well as other specific strains being present less in depression.

A study by Taniya et al. (2022) has found the colonization of the microbiome, early dysbiosis of the microbiota, too much usage of antibiotics and stress to impact the CNS through producing neurotoxins. All these factors impacting the CNS have been shown to possibly contribute to autism spectrum disorder.

Studies have also found a possible role for the nasal microbiota in the onset of disease in the central nervous system. Several distinct bacteria from the nasal microbiota have been found to correlate with the prevalence of Alzheimer’s disease. One possible pathway was via the production of a toxin, which can cause Alzheimer’s disease via entering the central nervous system (Thangaleela et al., 2022).

A meta-analysis conducted by Toh et al. (2022) looked at possible connections between the gut microbiome and Parkinson’s disease (PD), investigating results from conducting a meta-analysis. They found that microbiome composition significantly differed between PD patients and controls, with consistently increased abundances of *Megasphaera* and *Akkermansia*, and reduced *Roseburia*. This study highlights the connectedness of the gut microbiome and diseases linked to the CNS.

Previously mentioned studies have underscored the microbiome’s impact on various bodily functions. These aspects highlight the microbiome's dynamic nature and its strong connection with host physiology, particularly through the central nervous system and gut-brain axis. The microbiome's influence extends beyond gastrointestinal health, with previously discussed research showing its likelihood of impacting neurological conditions such as anxiety, depression, and even Parkinson’s disease. Given these diverse impacts, exploring how the microbiome may contribute to migraine and their interconnections is of great interest.

The overall connection between migraines and the microbiota

Overview

Studies on connections between the microbiome and a wide array of diseases have been an ongoing field of research, yielding a lot of results confirming the beliefs of the microbiome influencing disease. The field of the microbiome and its interplay with migraine has also been increasingly growing, producing interesting results as well. Intriguing connections between primarily the gut microbiota and migraines have been found, but also the oral microbiota seems to play a role. Additionally to these more prominent microbiota in migraine research, potential relations between other microbiota is also of great interest. The nasal microbiota holds diverse microbial communities and is in close proximity to the brain. Sinus infections or inflammation in this part of the body might affect the beginning of migraines, as these are known migraine triggers. Also microbiota other than the gut, such as the oral microbiota could have possible connections with the onset of migraines, as the microbes in this region also interact with the immune, hormonal and nervous system of the body. Disruptions by any of the previously mentioned microbial communities could contribute to the prevalence of migraines and are thus interesting to review.

The effect of different microbiomes on migraine can be explained by distinct general mechanisms through which the microbiota might influence migraine occurrence. For the next section in this review the two main mechanisms for migraine prevalence are; inflammation together with immune modulation and metabolic pathways.

Inflammation and immune modulation

One way the microbiome can possibly affect the onset of migraine is through the immune system. Factors resulting from the immune system such as cytokines and the inflammation resulting from this can possibly influence or result in migraine symptoms. To understand the role of inflammation and immune modulation, a quick overview of the immune system is important. The immune system consists of two main arms that work with interplay to combat infection and disease; the innate and adaptive immunity.
The innate immunity acts as an immediate response towards infections and consists of a wide array of components, including macrophages, mast cells and natural killer cells. The adaptive immunity acts as a long-term response which builds up memory of previously handled infections. This part of immunity consists of B cells, T cells and dendritic cells.
The way the components of the innate immunity get recruited is through the secretion of cytokines, which is also a measure of infection used in research.
The immune system can be affected by an array of factors, including environmental factors, age and exercise, but also the microbiome is a known influence on the immune system.
Since the implementation of germ-free animals in research, it has become clear that the microbiome plays a role in multiple immune functions and a lack of microbiota can even cause a significant deficiency in the immune system (Lambring et al., 2019; Shi et al., 2017). In previous research the role of the microbiome in several aspects of immunity has been acknowledged. Among these are T cell production, cytokine production, maintenance of homeostasis as a whole and the regulation in general of the immune system (Lambring et al., 2019).

According to Shi et al. (2017), multiple studies conducted using germ-free mice have shown that the intestinal microbiome plays a key role in harboring the function of the mucosal immunity. Germ-free animals have lower levels of regulatory T cells as well as a lower production of intraepithelial lymphocytes compared to specific pathogen free animals. These are both markers of the immune system. Another test found a possible decrease of angiogenin-4, a type of protein used as an agent against microbes in the gut, in germ-free mice compared to conventional mice. This again is an indication that the microbiome influences the immune system (Shi et al., 2017). Another study found reduction in the levels of pro-inflammatory factors in Peyer's patches and the mesenteric lymph nodes after administration of prebiotics, while immunoglobulin A levels were increased in feces. Also several other factors involved in the immune system, including interleukins and interferons. All these changes suggest again the interplay between the immunity of the intestinal mucosa and the microbiome of the gut (Shi et al., 2017).

A study by Carasi et al. (2015), studying the effects of *L. kefiri* strains on the gut microbiome and the intestinal mucosa, found that presence of the strains caused for secretion of a selection of proinflammatory Th1 mediators. Along these mediators are several interleukins and tumor necrosis factors. The study did also mention the fact that the results were to be expected, as the upregulation of the proinflammatory cytokines found in their study were found to be upregulated by probiotic bacteria in the research of other authors as well.

Research on the connection between the immune system and migraine also indicates a potential role for inflammation in the onset of migraine. A study by Fu et al. (2023) did research on the causal connection between inflammatory cytokines and migraine for which they used the genetic data retrieved from a GWAS. This study looked at 41 inflammatory cytokines and their causal relationship to migraine. The results showed no clear evidence of migraine having an effect on any of the inflammatory cytokines but did suggest a potential role for hepatocyte growth factor in the onset of migraine. Also IL-2 was found to be a probable influence later on in the progression of migraine. These two cytokines were identified as effectors of migraine and therefore potential targets in therapeutics. A study by Hubel et al. (2015) found that hepatocyte growth factor contributes to immune regulation through HGF/Met-signaling. The study claimed an effect of HGF/met-signaling on the ability of dendritic cells to differentiate and thus convey their function. Looking at the results from these two studies, there seems to be an evident effect of the immune system on migraine. Both studies conclude that further research is warranted and should be conducted in more cohorts.

Pavelek et al. (2020) compared immune parameters in episodic migraine (EM) patients and healthy controls. EM patients were shown to have higher levels of several immune cells, including lymphocytes, CD3 T cells, CD8 T cells, and CD4+ TEMRA cells. These cells are associated with pathogen protection and inflammation. The study found significant correlations between CD4+ TEM cells and migraine severity, suggesting that CD4+ TEM could be a biomarker for assessing migraine severity. The findings indicate CD4+ TEM is likely to be an important parameter, highlighting the need for further research to validate it as a potential biomarkers.

A case control study by Martami et al. (2018) found significantly higher levels of TNF-α in migraine patients compared to healthy controls. Their research again highlighted a correlation between the immune system and migraine.

Other studies have shown higher levels of both interleukin 1β and 6 in migraine patients, together with lower levels of interleukin 10, relative to healthy controls (Biscetti et al., 2021). The study by Biscetti et al. (2021) concludes that the immune system does play a role on migraine.

All previous studies mentioned above have found either a connection between the microbiome and the immune system, or a probable effect of the immune system on migraine. This raises suspicion of either a direct or indirect role of the microbiome on migraine through the immune system through multiple possible cytokines, as listed above.

Metabolic pathways

Next to the influence of the immune system, metabolic effects seem be of interest. As the microbiome is a community of diverse microbes, metabolism is one of its major functions. There are a lot of different compound resulting from metabolism, which though other pathways could possibly affect the onset of migraine. Products arising from the metabolic processes include short chain fatty acids (SCFAs), an array of peptides and even neurotransmitters among the likes of serotonin can be influenced by the microbiome. Contrary to the previous section, highlighting different factors influenced by the microbiome or influencing migraine separately, this section aims to connect specific metabolites to both. Nitrate containing metabolites have been shown to trigger migraine (Gonzalez et al., 2016), calling for the connection between the microbiome and migraine through metabolites to be investigated further.

Resulting from the fermentation of food components by gut bacteria, SCFAs among the likes of butyrate, acetate and propionate get produced. The study by Sanna et al. (2019) has shown connections between the concentration of SCFAs and obesity, both positive and negative, depending on the type of SCFAs. The study also showed that a shift in the microbiota affecting specific SCFA production can affect the risk of type 2 diabetes. This highlights the ability of the microbiome to affect disease through possibly favoring types of SCFAs as a result of the biota's composition.

Research by Lanza et al. (2021) found that SFCA was capable of reducing the concentrations of IL-6 and IL-8. As said before, interleukin 6 is involved in migraine attacks. Evidence shows that interleukin 8 is involved as well, and the concentration of these two interleukins are significantly higher for migraine patients compared to healthy controls. As results from the study from Lanza et al. (2021) show a strong decrease in both interleukins after administration of SCFAs, this indicates that SCFAs can influence the onset of migraine. This study was conducted in mouse models, calling for reproduction in models more representative of the human system.

Another possible metabolite through which the microbiota can influence migraine is calcitonin gene-related peptide (CGRP). CGRP is a protein related to pain. Another mouse model study conducted by Pujo et al. (2023) found germ-free mice to produce more CGRP, indicating the influence of the microbiota on CGRP levels and the gut pain sensitivity. The study also mentioned that central mechanisms are likely to be involved, indicating the possible complexity of the cascade. CGRP has also been linked to migraine. Research Cady et al. (2009) found that concentrations of saliva CGRP were higher in migraine patients. This study is however conducted over a cohort of 22 subjects, which does raise the need for reproduction in a bigger cohort. A more recent study by Wattiez et al. (2020) recognized drugs targeted at the receptor of CGRP or directly at CGRP are effective in treating migraine symptoms. From this it can be assumed that CGRP does have an effect on migraine and the microbiota effects migraine, inferring another possible connection between the microbiota and migraine.

Another way the microbiota can possibly influence and or trigger migraine attacks is by the neurotransmitter serotonin. As research has shown serotonin to affect migraine symptoms (Hamel & Currents, 2007) and an approximate amount of 95% of the bodies serotonin is provided by the gut (Appleton, 2018), a connection is highly probable. The microbiome of the gut can affect serotonin through multiple ways, as serotonin is metabolized in a number of steps (Potter et al., 2023). *Bifidobacterium* is able to stimulate the production of serotonin by upregulating the metabolism of tryptophan (Potter et al., 2023; Fang et al., 2022). The effect of sumatriptan on migraine attacks has been studied for a long time and results have shown that sumatriptan is an effective treatment for migraine symptoms, with up to 79% of 109 patients experiencing a decrease in symptoms (“Treatment Of Migraine Attacks With Sumatriptan”, 1991). Sumatriptan is a selective antagonist for the serotonin receptor, causing the positive results of sumatriptan on migraine to indicate serotonin plays a significant role in migraine attacks. As discussed before, because of the effect that the microbiome has on serotonin in the body it is highly likely to influence migraine through this metabolite as well.

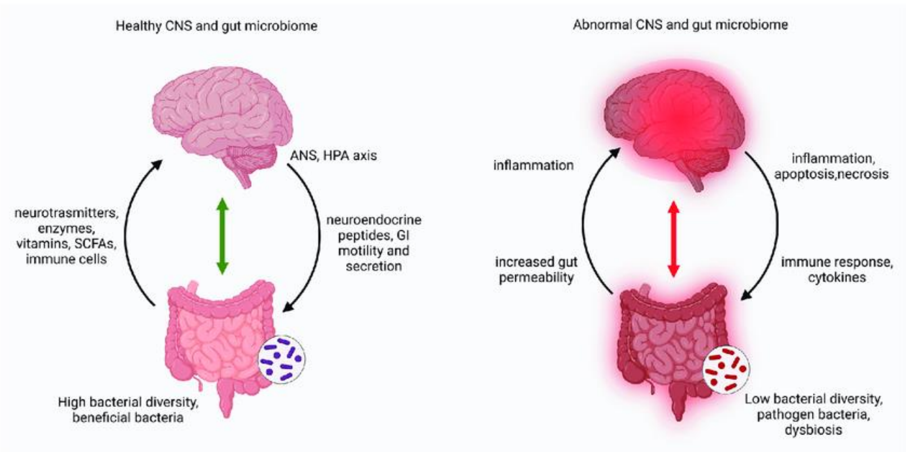

Figure 1. Bidirectional connection between the brain and the gut microbiome in both a healthy and abnormal state. CNS, central nervous system; ANS, autonomic nervous system; HPA, hypothalamic-pituitary-adrenal; SCFAs, short-chain fatty acids; GI, gastrointestinal (Spekker & Nagy-Grócz, 2023).

A more direct connection between migraines and the microbiota

Besides the previously discussed overall connections between the microbiota and migraine, recent studies have been conducted investigating more direct connections between migraines and the microbiota. Studies have shown direct connections between the two for both previously describes topics, inflammation together with immune modulation and metabolic effects. Another additional connection between the microbiota and migraine is the composition of the microbiome. Studies have shown that a difference in microbiota does correlate with migraine onset, as will be discussed.

Inflammatory effects

More direct associations between the gut, the immune system and the migraine have been found in recent research by Lee et al. (2024). This study based on the population of North Korea found migraine to be significantly correlated to developing inflammatory bowel disease. As inflammatory bowel disease is characterized by chronic inflammation of the gastrointestinal tract, this suggests the direct interplay between the gut microbiota, the immune system and migraine prevalence.

Metabolic effects

The previous section provided recent findings on both the connection of the microbiome on metabolic effects and the effects of these on migraine. Although a direct connection seems probable, these are merely assumptions. Research has been done on the direct connection between the two. Kang et al. (2021) has investigated if migraine-related hyperalgesia is affected by the gut microbiome in mice. The study compared nitroglycerin-induced hyperalgesia in mice with different gut microbiota profiles. It also examined the effect of transplanting gut microbiota from a migraine patient versus a healthy control on recipient mice. The study found that the gut microbiome does effect migraine related to hyperalgesia and the basal sensitivity of the host.

Other evidence found that changes in the structure of the gut microbiota can influence metabolism of the host, and the function of the microbiota might be an important mechanism for effecting migraine through specific medicine (Wen et al., 2019).

Composition of the microbiota

Studies have also investigated a more direct connection between the microbiome and migraine. Some studies have done this by using dietary interventions to try and affect the microbiota's composition, some have used probiotic supplements to alter the microbiota, and some have carried out a fecal transplantation to do so.

Results from previous research have shown that there are connections between the composition of the microbiota and migraine prevalence. A study by Gonzalez et al. (2016) found that individuals with migraine attacks were shown to have elevated levels of oral microbes that reduce nitrate, nitrite and nitric oxide. Nitrates are known to be migraine triggers, causing microbes that produces these compounds to be highly likely to induce migraines.

Results from a metagenomic shotgun-sequencing study found that the metabolic functioning of the gut microbiota and species diversity was significantly decreased in migraine patients. Additionally, the *Clostridium* species were found to be enriched in migraine patients (Chen et al., 2020).

A different study found another different strain to possibly affect the onset of migraines. An infection by the Helicobacter Pylori strain has been shown to be significantly linked to migraine in the presence of dyspepsia. The study by Akbari et al. (2016) found Helicobacter Pylori and migraine to be highly prevalent in individuals with dyspepsia. Migraine also seemed to be significantly related with peptic and duodenal ulcers. This specific study also stated migraine could be more complex than just a brain related disorder.

Affecting migraine prevalence with dietary changes is also likely to be possible. A diet composed of IgG antibodies for food antigens has been shown to reduce migraine onset (Alpay et al., 2010). This study showed significantly less migraine attacks and days of migraine following during the period of the elimination diet. The study did have a small sample size but does indicate that the diet based on antibodies against food antigens is effective for preventing migraine.

Furthermore, the usage of probiotics in order to affect migraine onset has been investigated using a probiotic mixture consisting of 14 strains. After administering the probiotics during a 10-week period to migraine patients, the prevalence of migraine reduced significantly in migraineurs compared to the control group (Martami et al., 2019). This study was conducted over a cohort of 39 patients, warranting further research in larger cohorts to validate the promising results. Despite the small cohort, the results do indicate probiotics to be a possible method to relieve migraine symptoms through altering the microbiome.

Discussion

The relationship between the microbiome and migraine is a continuously expanding field of research, shedding light on the mechanisms through which the microbiota may influence migraine pathophysiology. This paper aims to review the literature on these relationships and explore possible new connections by focusing on the roles of inflammation and immune modulation, metabolic pathways and more direct connections involving the composition of the microbiome. This study demonstrates a likely correlation between the onset of migraine and the microbiome via both the immune system and metabolic pathways. Additionally, more direct and established connections are analyzed.

A significant body of research has found multiple overlapping inflammatory factors produced in the microbiome and affecting the prevalence of migraines. Multiple studies have shown factors related to the immune system to be present in higher levels in migraine patients. Also research has reported a direct connection between the microbiome and migraine, indicating that there is a bi-directional relation possible between the two. As a result of these findings, the activation of the immune system and all effects that result from this are highly likely to affect migraine onset and symptoms.

Beyond immune modulation, specific metabolites affected by the microbiome have been found to affect migraine onset. Literature shows an effect of the microbiome on host metabolism through the production of metabolites such as short-chain fatty acids (SCFAs), peptides and neurotransmitters. These metabolites have in turn been shown to affect migraine onset, indicating host metabolism to affect migraine onset through its variety of products and pathways.

The composition of the microbiota has been explored as a more direct connection. Expanding research has found the composition of microbiota and the prevalence of different strains to possibly have an effect on the onset of migraines.

In conclusion, the microbiome appears to exert multifaceted effects on migraine through inflammation, immune modulation, metabolic pathways, and microbial composition. Diet and probiotics are also found to impact migraine onset. Expanding research underscores the interconnectedness between gut health and neurological conditions, including migraine, suggesting that strategies targeting the microbiome could offer novel therapeutic avenues. This study used literature to link the microbiome to migraine, supported by both experimental and clinical data. However, limitations include the predominance of observational studies and the need for more randomized controlled trials to establish causality and therapeutic efficacy. Another limitation is the usage of small cohorts and the wide variety of effects impacting migraine onset, making it hard to conclude whether or not certain factors are the main contributors to a migraine attack. Based on the findings, future research should prioritize longitudinal studies to investigate temporal relationships between microbiome changes and migraine episodes. Studies should be reproduced using larger cohorts, considering the environmental effects on migraine. The field of research reviewed shows an expanding body of evidence of connections between the microbiome and migraine, warranting further research elucidating the specific mechanisms underlying these connections.

Afterword

As our understanding of the microbiome's impact on migraine is extended, the insights gained from this study are aimed to expand our knowledge of how gut microbes influence migraine susceptibility and pathology. Further research in this field promises to uncover novel therapeutic strategies and personalized approaches to managing migraine disorders, enhancing the quality of life for individuals affected by this debilitating disorder.

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