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Review Article

Exploring The Connection Between the Gut Microflora and Brain Aneurysms: A Comprehensive Review

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Abstract

Objective: The gut microbiome has evolved as a considerable factor in cerebral aneurysm formation through a complex and multifaceted relationship. This would uncover potential insights into how dysbiosis and inflammation may contribute to the development of an aneurysm and subsequent rupture. This article aims to shed new light on our understanding of this intricate biological interplay.

Results:

A link between the gut microbiome and cerebral aneurysms was observed. The dysbiosis in the gut microbial community can cause inflammation and metabolic disorders, elevating the risk of ruptured aneurysms. Inflammation triggers cerebral aneurysm formation and rupture. There appears to be a significant difference in the microbial flora between patients with stable and unstable unruptured intracranial aneurysms.

Conclusion:

The maintenance of overall health depends on the gut microbiome, which also may contribute to developing cerebral aneurysms. Any changes in microbial metabolite production or dysbiosis can lead to inflammation and metabolic disorders that increase susceptibility to aneurysm formation and rupture. By conducting further studies exploring the link between gut microbes and this condition, new preventive as well as therapeutic measures could be developed.

Keywords: gut microbiome; intra-cranial aneurysm; dysbiosis; gut-brain axis

Introduction

The human gut microflora, a complex ecosystem of microorganisms, has emerged as a critical factor in maintaining overall health [1]. Human-associated microbiota refers to a complex ecosystem of microorganisms comprising a wide variety of bacteria, archaea, viruses, protozoa, fungi, and eukaryotic microbes [2]. Gut microbiota produces different metabolites, playing an important role including homeostasis, signaling, metabolism, immune regulation, and immune- inflammatory axes [3-5]. Dysbiosis is any alterations in the composition of resident commensal communities relative to the community found in healthy individuals [6]. Bacteroides and firmicutes are the main bacterial phyla found in stool samples, and Proteobacteria and Actinobacteria are small portions but present in most of the population [6]. Dysbiosis in the gut microbiome or alterations in the microbial metabolite production can lead to various diseases, including neurodegeneration, nervous system dysregulation, neurological disorders like Parkinson's disease and multiple sclerosis, digestive, metabolic, psychiatric, allergic, rheumatologic, atherosclerotic disorders and cancers where inflammation and inflammatory mediators play an essential role in determining of the progression and severity of the disease [7, 8]. Recent studies have elucidated an intricate relationship between the gut microbiome and several neurological disorders. Chronic inflammation is one of the important conditions that may lead to an aneurysm rupture by infiltration of cells and cytokines [9, 10]. Gut microbiota is a factor that affects the course and severity of human inflammatory disorders [9, 10].

The gut microbiome is associated with cardiovascular diseases such as atherosclerosis [11-13]. The gut microbiome also plays an important role in hypertension and heart failure [14-16]. Modulation of metabolic and immunoregulatory axes are the pathways through which gut microbiome affects illnesses' course and severity [10, 17, 18]. Diet has the most significant effect on determining the diversity and composition of the gut, and other environmental factors are lifestyle, physical activity, smoking, and

alcohol [17, 19, 20]. The "gut-microbiota-brain" (GBA) axis is a critical pathway in humans and animals. It is defined as a network of connections and interactions involving several complex systems and organs, including the central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), and hypothalamic pituitary adrenal (HPA) axis. This axis enables bidirectional communication between enteric microbiota and the brain [21].

This neuro-immuno-endocrine axis uniquely maintains gastrointestinal, CNS, microbial metabolism, and homeostasis [22, 23]. Several studies have demonstrated that gut microbiota significantly impacts GBA, interacting with various pathways, such as locally with intestinal cells and ENS and directly with CNS through neuroendocrine and metabolic pathways [8]. Recent studies have elucidated the intricate relationship between the gut microbiome and several neurological disorders, including ischemic stroke and aneurysms. Furthermore, the gut microbiome is associated with the progression and modulation of neurological disease outcomes. Unruptured cerebral aneurysms (CAs) affect 3-5% of the general population. Studies suggest that gut microbiota dysbiosis and inflammation may contribute to the pathogenesis of brain aneurysms. Inflammatory cells, markers, and mediators are also associated with the increased risk of ruptured aneurysms [24]. Inflammatory alterations that participate in CA formation and rupture are leukocyte infiltration, endothelial dysfunction, phenotypic modulation, loss of smooth muscle cells (SMCs), vascular remodeling, cell death, and macrophage (M1/M2) imbalance [25]. A recent hypothesis suggested a significant difference in the kind of microbiome profile between patients with stable and unstable unruptured intracranial aneurysms (UIAs). This difference can result in chronic inflammation and pathophysiological alterations in the aneurysm wall, eventually resulting in ruptured aneurysms (RAs) [9]. Although the relationship between the gut microbiome and brain aneurysms is not yet fully comprehended, the emerging evidence underscores the importance of investigating this association [26]. Understanding the role of the gut microbiome in the development and progression of brain aneurysms could lead to innovative preventive and therapeutic approaches for this condition [27]. Therefore, this narrative review will provide an updated overview to clarify the relationship between the gut microbiome and cerebral aneurysms.

Cerebral aneurysms and gut microbiome

The gut microbiome is a complex ecosystem of microorganisms that is crucial in maintaining overall health. Recent studies have implicated the gut microbiome in various neurological disorders, including cerebral aneurysms (CA) [28]. An unruptured intracranial aneurysm (UIA) is a life-threatening condition with a 3% prevalence. Rupture of UIAs is detected in 80-85% of subarachnoid hemorrhages, which is associated with catastrophic complications [9, 28, 29]. Several genetic and environmental factors play an important role in developing ruptured aneurysms (RAs) [9]. An imbalance in the proportion of gut flora has been suggested to be associated with an intracranial aneurysm [10]. For instance, Shikata et al. performed an animal model study and demonstrated that the administration of antibiotics leads to the depletion of the gut microbiome and the reduction of macrophage infiltration and mRNA levels of inflammatory cytokines [10]. The gut microbiome depletion led to a reduced incidence of intracranial aneurysms (Table 1) [10]. Li et al. demonstrated that Hungatella Hathewayi reduces the taurine levels, a protective against intracranial aneurysm, and could develop an intracranial aneurysm in mice [28]. Kawabata et al. showed that the abundance of Campylobacter in the gut microbiome is associated with the rupture of UIAs [9]. Sun et al. exhibited that the Ruminococcaceae and Clostridiales families are higher in symptomatic vs. asymptomatic UIA patients [29]. They also demonstrated a significant decrease in propanoate metabolism and increased peptidoglycan biosynthesis in the gut microbiome of symptomatic patients [29]. Correspondingly, previous studies demonstrated that Plasma Trimethylamine N-oxide (TMAO) levels were elevated in AAA patients, and this was positively correlated with abdominal aneurysm growth rate [30-32]. A study also showed that a diet high in choline significantly increased plasma TMAO levels, abdominal aortic diameter, and AAA incidence in an AAA mouse model [32]. The gut microbiota's role in AAA formation and progression was demonstrated by the significant reduction in plasma TMAO levels and attenuation of AAA when the gut microbiota was suppressed with antibiotics [31, 32]. Additionally, providing TMAO to mice lacking intact gut microbiota increased plasma TMAO levels, aortic diameter, and AAA incidence, indicating that TMAO contributes directly to AAA pathogenesis. These findings suggest that interventions targeting TMAO or the gut microbiota may have therapeutic potential in preventing or treating AAA [31, 32]. Nonetheless, Emonds et al. demonstrated, despite of initial assumption that individuals with elevated TMAO levels would be more susceptible to SAH, actually observed that patients with SAH had lower levels of plasma TMAO upon admission to the hospital when compared to control subjects who had nerve, nerve root, or plexus disorders [33]. Identifying any distinct pattern in the plasma TMAO levels of SAH patients seems to need further comprehensive research.

Table 1. Association between the Gut microbiome and cerebral aneurysms

Study	Year	Type of study	Cases	Outcome
Kawabata et$_{al}$ (9)	2022	Case-control study	61	The relative abundance of Campylobacter and Campylobacter ureolyticus was reported to be higher in ruptured than unruptured
Li et al. [34]	2020	Case-control	140	By reduction in taurine level, Hungatella Hathewayi plays as protective agent against intracranial aneurysm
Sun et al. [29]	2022	Case-control	132	The Ruminococcaceae and Clostridiales families are higher in symptomatic than asymptomatic UIA patients

Table 1: Association between the Gut microbiome and cerebral aneurysms

Mechanism of CA formation and pathogens

The gastrointestinal tract is an important immune organ and includes 70% of the immune system [35]. The gut-microbiota-host interaction plays an important role in the maturation and modulation of the immune system [36]. The inflammatory process that leads to the development of CAs is started by a hemodynamic insult that causes matrix metalloproteinases (MMPs)-mediated degradation of the extracellular matrix and apoptosis of smooth muscle cells (SMPs) that are the main cells of the vessel wall [25]. Overall, these processes weaken the cell wall and aneurysm formation and, eventually, rupture of the aneurysm [25]. The two main cells participating in the process are macrophages and SMCs [25]. Previous studies demonstrated decreased levels of SMC (type 22a) due to the release of inflammatory cytokines and MMPs by macrophages with exceeding additional inflammatory cells, which leads to abdominal aorta aneurysms [25, 37, 38]. Moreover, Xie et al. concluded abundance of Akkermansia, Odoribacter, Helicobacter, and Ruminococcus might be dominant in the progression of AAAs in mice models [39]. In addition, increased Lactobacillus and

Prevotella copri with decreased Bifidobacteria and Bacteroides levels lead to chronic inflammatory diseases such as colitis or rheumatic arthritis [40]. Meanwhile, inhibition of MMPs and monocyte chemoattractant protein-1 (MCP-1) prevents CA formation or its progression [41, 42]. M1 and M2 macrophages possess proinflammatory and anti-inflammatory characteristics, respectively, and both are present in CAs in an equal ratio [25]. In RAs, an increase in M1 cells is observed, and the M1/M2 imbalance leads to the rupture [43].

SMCs are the main matrix-synthesizing cells in the vessel wall and are mostly located in the media layer [25]. The media layer provides the integrity of the vessel wall, and its thinning results in the CA formation [25]. During the early phases of CA formation, SMCs migrate to the intima layer and undergo phenotypic modulation via tumor necrosis factor-α (TNF-α), Kruppel-like transcription factor 4 (KLF-4), and interleukin-1β (IL-1β) that promotes inflammation and matrix breakdown [25, 44-46]. On the other hand, Zhang et al. found higher levels of Proteobacteria, Enterobacteriaceae, Anaerostipes, and Coprococcus in patients with abdominal aorta aneurysms with a direct effect on SMC integrity [47]. Furthermore, Ito et al. presented that the abundance of B. adolescentis decreased in patients with AAA related to loosening vessel walls [48]. The modulated SMCs are not able to provide the integrity of the vascular wall and synthesize collagen [25]. In case of rupture, SMCs are decreased and undergo apoptosis in the media layer, and the activity of caspases is increased [24, 49, 50]. Another cell that has a role in the pathogenesis of CAs is the mast cell [25]. Mast cells are major immune parts that actively play roles in neurodegenerative CNS diseases such as chronic pain, Parkinson's disease, and neurovascular [51- 53]. Dysbiosis in the gut-brain axis and an increase in the number of mast cells are observed during CA formation, and their degranulation results in the induction of the expression and activation of the MMPs [25]. A study demonstrated that the upregulation of mast cells is more in RAs than UIAs [43]. The inhibition of mast cells results in the prevention of CA progression [54].

Inflammatory cytokines play an important role in CAs, and TNFs and ILs are the most important ones [26]. TNF-α is the most important cytokine in the CA formation process. It activates neutrophils and lymphocytes, increases the permeability of vessels s the metabolic activity of tissues, and promotes the release of other cytokines [46, 55]. TNF-α promotes inflammation and apoptosis in vessels; subsequently, the vessel wall's weakening occurs, and the CAs are developed [46, 56]. The inhibition of TNF-α reduces the rupture rate of CAs in the animal model [46, 57]. ILs act on immune cells and lead to immune cells' maturation, activation, proliferation, and regulation [58]. IL-1 is an important factor in inflammation, immune regulation, and neurodegeneration [58]. IL-1β promotes the infiltration of immune cells and the formation of aneurysms [46]. Gut microbiota affects the formation of CAs via modulation of inflammation within the aneurysmal walls [10]. Another mechanism is attributed to the transmigration of gut bacteria into the cerebral vessels [10]. Shikata et al. induced gut microbiota depletion through an oral antibiotic cocktail of ampicillin, metronidazole, neomycin, and vancomycin. The gut microbiota depletion significantly reduced the development of CAs by means of decreasing macrophage infiltration and the expression of pro-inflammatory cytokines such as IL-1b and IL-6 in vascular wells [10]. Kawabata et al. demonstrated that cells infected with Campylobacter ureolyticus produced significantly higher levels of IL-8, MMP-8, MMP-9, myeloperoxidase, and human neutrophil elastase. Therefore, enhanced cytokines, neutrophil-derived proteolytic, and oxidative stress by Campylobacter may promote vascular remodeling of CA walls and ultimately, combined with hemodynamics and genetics, change UIA into RA [9].

Conclusion:

There is a potential link between an imbalance in gut flora and an increased risk of cerebral and abdominal aneurysms. Dysbiosis in the gut-brain axis results in an inflammatory process leading to aneurysm formation involves the degradation of the extracellular matrix and apoptosis of SMCs, which can be inhibited by targeting MMPs and MCP-1. Interventions targeting specific gut metabolites increased in intra-cranial neurovascular accidents or the gut microbiota may have therapeutic value in preventing or treating aneurysms. Further research is necessary to fully understand the relationship between the gut microbiome and aneurysms.

Abbreviations:

PICO = Population-Intervention-Comparison-Outcomes

SAH = Subarachnoid hemorrhage GBA = Gut-microbiota-brain

CNS = Central nervous system ANS = Autonomic nervous system ENS = Enteric nervous system

HPA = Hypothalamic pituitary adrenal CA = Cerebral aneurysms

SMC = Smooth muscle cells

UIA = Unruptured intracranial aneurysms RA = Ruptured aneurysms

WOS = Web of Science

NOS = Newcastle-Ottawa Scale TMAO = Trimethylamine N-oxide AAA = Abdominal aortic aneurysms MMP = Matrix metalloproteinases

MMP-8 = Matrix metalloproteinases -8 MMP-9 = Matrix metalloproteinases - 9

MCP-1 = Monocyte chemoattractant protein-1 TNF- α = tumor necrosis factor-α

KLF-4 = Transcription factor 4 IL-1β = Interleukin-1β

IL-1 = Interleukin-1 IL-8= Interleukin-8

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