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Review Article

Targeting gut dysbiosis as a means to enhance recovery from surgical brain injury

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ABSTRACT

Background: Surgical brain injury (SBI) impacts roughly 800,000 people who undergo neurosurgical procedures each year. SBI is the result of unavoidable parenchymal damage, vessel disruption, and thermal injury that is an inherent part of all neurosurgical procedures. Clinically, SBI has been associated with postoperative seizures and long-term neurobehavioral deficits. Current therapies are aimed at providing symptom relief by reducing swelling and preventing seizures. However, there are no therapies aimed at reducing the extent of SBI preoperatively. The microbiome-gut-brain axis may serve as a potential target for the development of new preventative therapies due to its extensive involvement in central nervous system function.

Methods: An extensive literature review was conducted to determine whether there is a potential role for dysbiosis treatment in reducing the extent of SBI.

Results: Treatment of gut dysbiosis deserves further exploration as a potential means of reducing the extent of unavoidable SBI. Dysbiosis has been correlated with increased neuroinflammation through impaired immune regulation, increased blood-brain barrier permeability, and increased production of reactive metabolites. Recently, dysbiosis has also been linked to acute neurological dysfunction in the postoperative state. Importantly, treatment of dysbiosis has been correlated with better patient outcomes and decreased length of stay in surgical patients.

Conclusion: Current literature supports the role of dysbiosis treatment in the preoperative setting as a means of optimizing neurological recovery following unavoidable SBI that results from all neurosurgical procedures.

Keywords: Dysbiosis, Microbiome gut-brain axis, Neuroinflammation, Surgical brain injury, Traumatic brain injury

INTRODUCTION

The human microbiota contains over 100 trillion cells and is comprised of a diverse array of bacteria, fungi, archaea, and viruses.[34] These organisms outnumber our own cells ten-fold and produce over 99% of the genes in our bodies.[25,27,28,38,58,71] Given the sheer volume and genetic potential of these organisms, research investigating the role of the microbiome in human health and disease has increased exponentially over the last two decades. One area that has garnered much attention recently is the microbiota-gut-brain axis (MGBA). The MGBA is a bidirectional communication system that enables the central nervous system (CNS) to communicate with the gut and vice versa. The communication between the gut and the CNS is controlled mainly

through the direct and indirect connection of the CNS and vagus nerve with the gastrointestinal tract's enteric nervous system (ENS). The ENS modulates gut motility, absorption, secretion, and blood flow, thereby providing an environment that is suitable for some organisms and incompatible for others. Conversely, the microbiota produces neurotransmitters and metabolites capable of affecting ENS and vagus nerve signaling.[10,52,74]

While the complexities of the MGBA are still being discovered, it has become clear that the relative diversity and abundance of certain species of organisms play a role in human health and disease. Disruption of the microbiota, so-termed dysbiosis, is the result of environmental disturbances from several factors. To date, stress, age, host environment, diet, medications (not limited to antibiotics), and maternal factors[46] have been shown to impact the gut environment through changes in motility, gut wall permeability, and nutrient abundance.[24] As such, each of these factors represents a potential source through which dysbiosis can develop.

The clinical impact of dysbiosis is extensive. Not only has chronic dysbiosis been linked to obesity, diabetes, IBS, and IBD, but more recently, it has also been correlated with numerous neurological disorders, including but not limited to autism spectrum disorder (ASD), Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis, depression, and anxiety.[24] More recently, research has shown that acute dysbiosis due to neurological injury and resulting MGBA disruption is associated with negative recovery outcomes following traumatic brain injury (TBI) in mouse models.[43,96] Therefore, preventing dysbiosis may serve to protect against acute and chronic neurological dysfunction following neurological injury.

Despite the evidence highlighting the important role of the MGBA in neurological function, there has been little investigation into the role of the MGBA in outcomes following surgical brain. The purpose of this review is to summarize the current evidence supporting the role of dysbiosis treatment in reducing the extent of surgical brain injury (SBI) and enhancing patient recovery from it.

SBI

SBI may result from neurosurgery due to unavoidable parenchymal tissue incisions, small vessel damage, tissue retraction, and burn injury due to electrocautery. Although efforts have been made to reduce SBI through the development of minimally invasive techniques, tissue injury is inevitable in the over 800,000 neurological procedures performed per year.[45] Because of this damage, neurosurgical patients may experience prolonged surgical complications and lifelong neurobehavioral deficits. The current postsurgical treatment encompasses neuroprotective strategies aimed at reducing edema, ischemia, and dysfunction through the use of osmotic agents, steroids, diuretics, and anti-seizure medications. Unfortunately, none of these agents have definitively been shown to decrease postoperative complications.

Numerous *in vivo* mouse models have concluded that SBI results in neuronal cell death, apoptotic changes, increased oxidative stress, and blood-brain barrier (BBB) disruption at the surrounding surgical site.[45] Ultimately, these pathological processes result in the activation of microglia, astrocytes, and macrophages, which deposit collagen in the formation of glial scars in the surrounding areas.[87] This scarring continues to undergo remodeling and reconstruction for years afterward, resulting in further neurological damage. These results support findings of long-term human studies which show progressive atrophy of brain structures following TBI, stroke, therapeutic lobectomies, and surgical treatment of subarachnoid hemorrhages.[9,12,30,31,39,78,84]

Current research has been directed at identifying specific therapeutic targets that may prevent SBI. Due to the nervous system's inability to regenerate tissue in a significant manner, to truly offer a clinical benefit for patients, therapies need to reduce the extent of SBI. Current investigational treatments for SBI have been identified based on two modes of thought: activation of neuroprotective mechanisms or inhibition of neuroinflammatory signaling before damage.

One promising therapy involves Slit2, which may play an important role in neurological recovery. Slit2 is a protein involved in neuronal and axonal development that is expressed at increased levels in the brain following SBI.[79] Treatment with recombinant Slit2 in a mouse model reduced SBI-induced BBB permeability due to an increased expression of BBB tight junction proteins, occludin, and claudin 3.[79] Another potential neuroprotective treatment being investigated is preoperative exposure to milk fat globule-epidermal growth factor B (MFGE8). MFGE8 is a neuroprotective signal that promotes phagocytosis, thereby eliminating apoptotic cells before the release of toxic signals. This attenuation of SBI-induced toxic signaling has been associated with decreased brain water content, cell death, inflammation, and neurological dysfunction.[79,101] Conversely, some investigators are looking at preconditioning with toxic substances as a potential means of decreasing neuroinflammation from SBI. Preconditioning with brief exposure to minor amounts of deleterious stimuli has been shown to stimulate tolerance toward future uncontrolled exposures of the same molecule.[1,70] In mouse models, preconditioning with PLA2 resulted in reduced edema, intra-operative bleeding, and improved neurological function following SBI.[94]

While these therapies show promise, their clinical utility is limited by several factors, including GI absorption, ability to

reach the CNS, off-target effects, cost, and general availability. Therefore, other therapeutic targets need to be explored.

TARGETING THE MGBA

The role of the MGBA in disease has become a focus in the neuroscience community within the last decade. Beginning in 2011, investigators showed that compared to control mice, germ-free mice grown in specific-pathogen-free conditions had less anxiety-like behavior.[57] Since that time, microbiota composition and dysregulation have been linked to the development of a wide range of neurologic conditions. The exact mechanism of interaction between the gut microbiota and the CNS and how this interaction contributes to disease has yet to be revealed. Nevertheless, research has identified several mechanisms in which this bidirectional communicating system may impact neurological function and disease development.

Modulation of autonomic nervous system (ANS)

Signaling within the MGBA is multifaceted, including direct and indirect signaling between the ENS and the vagus nerve part of the ANS. While the ENS is considered a branch of the ANS, it is also capable of functioning independently. The ENS is composed of over 20 different types of neurons (each with their own function) that interact to form the myenteric and submucosal plexuses.[92] Each plexus represents a complex network of glia, motor neurons, intrinsic sensory neurons, and interneurons that extend throughout the length of the GI tract to control all aspects of digestion, including peristalsis, sphincter tone, and enzymatic secretions.

The interaction of the ENS and ANS is achieved through a combination of direct and indirect mechanisms. ENS sensory and motor neurons provide direct innervation to the vagus nerve, thereby allowing the ENS to provide constant feedback on microbiota structure and function to the CNS. Furthermore, our microbiota may exert direct influence over CNS function. *In vivo* mouse models showed that anxiolytic *Lactobacillus* treatment was rendered ineffective in animals who underwent vagotomy.[35] In addition, introducing microbiota in a germ-free mouse model and/or altering the microbiota in antibiotic-treated control mice have demonstrated how the gut microbiota directly influences the levels of neuromodulators such as plasma levels of serotonin, tryptophan, and kynurenine and hypothalamic levels of vasopressin and oxytocin;[54,65,80] neurogenesis in the adult hippocampus;[62] normal myelination in the prefrontal cortex during early development;[42] and changes in neuronal excitability and action potentials in enteric neurons.[56]

These observed structural and functional changes are correlated with different clinical outcomes. First, dysbiosis at an early age leads to dysregulated stress responses through the prevention of hypothalamic-pituitary-adrenal axis maturation.[86] This manifests as increased anxiety, elevated ACTH and cortisol levels.[14,57] Second, vagal input to the CNS can initiate anti-inflammatory responses which are vital for the regulation of mood and cognitive function.[60] Dysbiosis may modulate this input, resulting in inhibition of anti-inflammatory processes and leading to mood changes. In addition, several CNS disorders such as PD, AD, and ASD are characterized by ENS dysfunction. The role of ENS dysfunction in the development and progression of these diseases is not well understood, but there is little doubt that the MGBA plays a contributing role. Based on the multitudes of study data that establish the importance of MGBA in neurologic disease, many researchers are now beginning to investigate how best to manipulate the microbiota to combat disease.

Modulation of neuroinflammation

The microbiota plays an important role in immune system development and regulation of neuroinflammation later in life. Increased neuroinflammation has been linked to the development and progression of several neurodegenerative disorders, including AD, PD, AIDS-induced dementia, and TBI.[32] Dysbiosis leads to disruption of the BBB and activation of microglial cells in the CNS, resulting in increased neuroinflammation, thereby furthering disease burden.

One of the most devastating impacts of neuroinflammation is its disruption of the BBB. Pro-inflammatory cytokines enter the brain through active transport, diffusion through permeable circumventricular organs, or through generation at the BBB in response to a peripheral signal.[55] Once in the brain, inflammatory cytokines can regulate the loss of BBB integrity.[61] In one study, researchers showed increased BBB permeability in germ-free mouse models.[13] This alteration in BBB permeability resulted in the ability of bacterial and cellular metabolites and bacteria themselves to access to the CNS and influence neurological function.[37] However, treatment of dysbiosis may be able to reverse BBB damage and restore its protective function. When researchers provided the germ-free mice with pathogen-free gut flora, BBB permeability was reduced.[13]

Notably, TBI also results in increased BBB permeability through unknown mechanisms.[32] This increase in BBB permeability is one of the main determinants of secondary brain injury characterized by edema, microglial activation, and inflammation. To date, no studies have been conducted to investigate whether treating dysbiosis in TBI patients results in restoration of BBB integrity and decreased secondary brain injury. Nonetheless, dysbiosis treatment has been shown to play an important role in restoring the BBB to its preperturbation status.[13] Therefore, it stands to reason that

dysbiosis treatment may also help prevent secondary brain injury following TBI, which has similar pathophysiological mechanisms with SBI.

Dysbiosis treatment may also prevent SBI-induced damage through mitigation of microglial activation. Microglia serves several important functions in the CNS. First, during development, they modulate neuronal development and synaptic connections to establish CNS circuitry.[2] Following the development, microglial plays an important role in CNS homeostasis. Microglia cells monitor the environment through their dendritic processes and respond accordingly when exposed to pro-inflammatory or anti-inflammatory cytokines. As such, disruptions in BBB permeability can result in microglial activation. Enhanced microglial activation due to neuroinflammation has been linked with numerous neurological disorders, including ASD, schizophrenia, major depressive disorder, PD, AD, and MS.

While a direct link between dysbiosis, microglial activation, and disease development has not been clearly established, there are numerous studies which support such a relationship. In one study, when PD mouse models were treated with fecal transplants from healthy mice, researchers observed decreased microglial activation and decreased motor deficits.[88] Similarly, when amyloid precursor protein (APP) transgenic germ-free mice undergo fecal transplants collected from control APP mice, the germ-free mice develop significant CNS accumulation of amyloid plaques.[94] β-amyloid is produced by *Escherichia coli*, *Salmonella enterica*, *Salmonella typhimurium*, *Bacillus subtilis*, *Mycobacterium tuberculosis*, and *Staphylococcus aureus* in clinically significant amounts. This exogenous β-amyloid crosses into the CNS, where it activates microglia resulting in increased production of ROS.[6]

Treatment of dysbiosis may act to decrease neuroinflammation through increased regulation of inflammation. Through investigations comparing germ-free mice to controls, researchers have shown the importance of the microbiota in the activation of and development of tolerance in T cells,[8] the development of antigen-presenting cells, neutrophil production and function, and natural killer cell differentiation.[97] Furthermore, research has revealed that certain bacterial populations can favor anti-inflammatory or pro-inflammatory states.[41] Colonization of the gut with segmented filamentous bacteria leads to increased production of Th17 cells, which produce IL-17, a pro-inflammatory cytokine.[77] Dysbiosis-induced alterations in cell populations and their resulting activity can result in increased production of cytokines. Clinically, this increase in pro-inflammatory cytokines has been linked with increased disease burden in MS mouse models.[19]

Conversely, treatment of dysbiosis can reduce inflammation and disease burden. Investigators showed that increasing the gut population of *Bacteroides fragilis* led to increased Treg cell regulation, which ultimately led to the suppression of pro-inflammatory IL-17 production.[77] In addition, oral administration of Polysaccharide A, a metabolite of *B. fragilis*, induced anti-inflammatory IL-10 and Treg cell activation resulting in decreased IL-17 cytokine production and improved clinical function for MS mouse models.[19] Nullification of IL-17 signaling has also been correlated with decreased neuroinflammation and increased neurocognitive outcomes in AD.[23] Similarly, a randomized, blinded study tested the use of specific probiotics (*Lactobacillus salivarius* UCC4331 and *Bifidobacterium infantis* 35624) versus placebo in 77 patients for 8 weeks. At baseline, these patients had a systemic IL-10/IL-12 ratio indicative of Th1 pro-inflammatory state. Of these patients, those who received Bifidobacteria decreased their pro-inflammatory state and had improvement of symptoms. Thus, these patients demonstrate that a specific change in the microbiota not only reduces inflammatory signaling but also contributes to improved clinical outcomes.[20]

Oxidative and nitrosative stress

Oxidative stress

Several *in vivo* studies have suggested a role for dysbiosis in increased OS and resulting CNS dysfunction. PD has long been linked with GI disturbances that precede neurological symptoms by years. When researchers analyzed the microbiome of PD patients, they found that there were significantly less H_2 producing bacteria.[63,66] Similarly, PD patients with high concentrations of H_2 due to overgrowth of H_2 producing bacteria had decreased neurologic symptoms.[75] H_2 functions as an antioxidant capable of reducing hydroxyl radicals. These results suggest that dysbiosis may lead to neuronal destruction through decreased H_2 production, which results in the increased presence of ROS. This was further supported by a study in rat models of PD, which showed treatment with oral solutions containing 50% saturated H_2 resulted in nigrostriatal degeneration was prevented or delayed.[36]

Based on the above results and the characteristic nature of the CNS which makes it more susceptible to damage by OS, treatment of dysbiosis may serve a critical role in preventing CNS damage from resulting SBI-generated OS. There are several characteristics of the CNS that makes it vulnerable to damage from ROS. First, the CNS has a high oxygen demand due to its almost complete dependability on oxygen phosphorylation for ATP production. Unlike other organ systems, the CNS is incapable of storing large quantities of energy due to its near-constant demand. As such, the CNS is always producing large quantities of ROS through continuous utilization of oxidative phosphorylation

for energy requirements.[29,72] Second, the CNS contains numerous molecules that perpetuate the formation of ROS, including iron, copper, and neurotransmitters capable of self-oxidation.[21,29,50] Third, the CNS contains reduced levels of glutathione which is needed for detoxification, cellular homeostasis, cellular signaling cascades, and cell differentiation and proliferation.[5] Fourth, the brain contains a high concentration of lipids which are extremely susceptible to oxidative damage.[3,7] When ROS reacts with lipids, it disrupts cellular signaling, cell membranes and leads to the formation of metabolites capable of disrupting protein structure and function.

Nitrosative stress

Dysbiosis directly and indirectly causes increased production of nitrosative stress through several different mechanisms. Reactive nitrogen species (RNS) production is linked directly to nitric oxide (NO) synthesis.[22] At physiologic levels, NO acts as an important intracellular signal in neuroprotective pathways such as cell proliferation, differentiation, and survival. However, high levels of NO can interact with ROS to form peroxynitrite, a highly reactive molecule that is capable of posttranslational modification of numerous proteins and inhibition of the electron transport chain. As a result, RNS can lead to decreased production of ATP, ultimately causing mitochondrial fragmentation and apoptotic cell death.

NO is produced by three different types of NO synthases (NOS) through the conversion of L-arginine to L-citrulline.[85] These enzymes are neuronal-NOS, inducible-NOS (iNOS), and endothelial-NOS. Bacteria directly and indirectly affect the production of NO in three main ways: (1) bacteria-induced inflammation activates iNOS,[64,85] (2) some bacterial species such as *Streptomycetes*, *Bacilli*,[91] and *Nocardia*[18] contain their own NOS and can produce exogenous NO, and (3) bacteria such as *E. coli* and *Lactobacillus plantarum* can metabolize nitrate and ammonium to nitrite, which is further metabolized by *E. coli* to produce NO.

Increased peroxynitrite production in microglial cells has been correlated with dysbiosis characterized by colonization of the gut by *E. coli, S. enterica*, *Salmonella typhimurium*, *Bacillus subtilis*, and *S. aureus*.[91] Furthermore, peroxynitrite provoked mitochondrial fragmentation has been correlated with the development of PD, AD, Huntington's disease, and amyotrophic lateral sclerosis.[69,91] When mouse models of PD (induced with methyl-4phenyl-1,2,3,6-terahydropyridine [MPTP] treatment) were treated with NOS antagonists, there was delayed substantia nigra compromise due to decreased formation of ROS and RNS[75] and inhibition of MPTP-mediated destruction of dopamine-containing neurons.[100]

TREATING DYSBIOSIS – WHICH METHOD IS BEST?

Dysbiosis is defined as the persistent imbalance in gut microbial communities. This imbalance has been linked to increased systemic inflammation and dysregulation. From a neurological perspective, dysbiosis results in dysregulation of the MGBA, leading to increased BBB permeability, increased ROS/RNS, neuronal conduction abnormalities, and neuroinflammation. Thus, treating dysbiosis may prevent or slow the progression of numerous neurological disorders. Probiotics, prebiotics, and dietary modifications have all been shown to treat dysbiosis and restore the gut to its predisturbed state. However, determining which treatment works best is still a point of debate within the scientific community.

Dietary modification

The composition of the microbiome is dependent on many factors, one of the most important being diet. From the time of our birth, our diet impacts our microbiome and consequently our health. Breast milk is rich in carbohydrates, nucleotides, cytokines, and immunoglobulins that are important for infant growth.[51] When compared to infants who were formula-fed, breast milk-fed infants had decreased gut colonization by pathological species such as *E. coli*, *C. difficile*, and *Bacteroides fragilis* and increased presence of beneficial species.[67] As we transition to solid food, our choice of sustenance and the amount of dietary intake guides the establishment of our microbiome. If dietary intake is not sufficient at a young age, it can cause disease. One study found altered bone morphology, stunted growth, and altered brain metabolism in mice who received microbiota transplants from malnourished children.[11]

Older individuals are also at increased risk of dysbiosis. Aging leads to natural immunosuppression and senescence, resulting in increased systemic inflammation and the development of disease. Furthermore, changes in digestion and motility affect microbiota communities. Unfortunately, many factors of dysbiosis in the elderly are irreversible. However, diet is an important modifiable determinant of dysbiosis and may serve as a potential treatment for those with or at risk for dysbiosis. One study analyzed the microbiota of 178 elderly individuals and found that there was a significantly decreased diversity of bacterial species.[76] Further analysis revealed that the severity of dysbiosis in these patients was dependent on diet. Fortunately, changes in diet have been linked with changes in microbiota. Researchers found that even if patients only change their diet for a short period of time (<24 h), it can lead to tremendous changes in microbiota composition.[26] Current investigation is centered on determining which diets may provide the most benefit for patients.

Diets high in unhealthy fats, protein, salts, and simplex sugars, so-called the western diet (WD), result in elevated levels of *Firmicutes* and *Collinsella* and decreased levels of *Bacteroides*.[73] These changes in microbiota composition have been linked to increased risk of obesity, depression, anxiety, and cognitive dysfunction.[59,73] One study revealed that consumption of a WD for only 3 days resulted in impaired spatial memory in rodents.[59] It has been suggested that through changes in microbiota composition, the WD can cause increased gut permeability, BBB dysfunction, and neuroinflammation.[47,59] In one prominent study, the decreased presence of *Bacteroides* that resulted from WD was associated with decreased conjugation of bile acids.[15] These unconjugated bile acids become charged in the distal colon and are capable of inflicting damage to the gut lining. This damage results in increased gut permeability, which has been linked with increased neuroinflammation.

Conversely, diets like a Mediterranean diet (MD) that consist mainly of fruits, vegetables, legumes, and whole grains have been linked to decreased systemic and neurological inflammation through changes in microbiota composition.[22,47,53] Namely, MD results in increased concentrations of *Bacteroides, Prevotella,* and *Bifidobacteria*, some of which have shown to play important roles in the development of neuropsychiatric diseases.[22,73] MD consists of high levels of omega 3 and omega 6 PUFAs which have been linked with decreased risk of developing depression.[17] When microbiota analysis was performed on patients consuming diets heavy in omega 3 and omega 6 PUFAs, researchers found increased concentrations of *Bifidobacterium* and *Lactobacillus*.[73] This change in bacterial population suggests that *Bifidobacterium* and *Lactobacillus* may play a major role in neuropsychiatric disease development.[73] This is further supported by studies that show the administration of probiotics containing *Lactobacillus* to patients with depression results in decreased symptoms of depression. In addition, *Bacteroides, Prevotella,* and *Bifidobacteria* are critical for the fermentation of carbohydrates into active metabolites and short-chain fatty acids (SCFAs). *In vitro* studies have shown that through activation of AMPK kinase, SCFAs play a crucial role in the regulation of lipid and cholesterol metabolism[83] which has been correlated with reduced incidence of neurodegenerative diseases.[81] Importantly, MDs are also high in many important prebiotics, which play an important role in the treatment of dysbiosis.

Prebiotics

Prebiotics are insoluble dietary fibers that serve to stimulate the growth of commensal bacteria to promote a healthy microbiota. Studies have revealed that decreased intake of insoluble fibers leads to a restricted microbiota, thereby inducing dysbiosis.[82] Clinically, prebiotics have been linked with several health benefits, including decreased body mass index and immune modification leading to decreased systemic inflammation.[40] More recently, the role of prebiotics in treating neurocognitive disorders has garnered interest.

Numerous prebiotics are being investigated for potential use in disease treatment; however, galactooligosaccharides (GOS) have become the focus of many investigators. GOSs are fermented mainly by *Bifidobacteria* and *Lactobacilli* bacteria in the gut.[73] As such, when used as a prebiotic, GOS induces increased gut colonization of these species. Clinically, administration of GOS has been linked with numerous health benefits, including an observed decrease in anxiety and depression-linked behaviors in mouse models.[93] Similarly, in healthy human volunteers, GOS led to decreased serum cortisol levels and decreased vigilance when presented with negative stimuli.[16] In another study, 10-week treatment with GOS in the elderly resulted in decreased inflammation revealed by fecal analysis.[99]

Importantly, GOS has been shown to reduced surgery-induced cognitive disfunction.[99] Mice were pretreated with GOS for 18 days before abdominal surgery. Compared to control animals, GOS animals had decreased neuroinflammation (decreased IL-6 and Il-4 in hippocampus) and cognitive impairment as revealed through object recognition tasks. When the microbiomes of these animals were analyzed, it was discovered that GOS treated animals had increased *Bifidobacteria*.[49] These results suggest that pretreatment of dysbiosis with prebiotics confers neuroprotection through the prevention of neuroinflammation.

Probiotics

Probiotics are living microorganisms that, when consumed, can provide many health benefits to the host such as antibacterial and antiviral effects,[44] reducing inflammation,[60] and restoring a healthy gut flora balance.

In addition, probiotics have been shown to have a beneficial impact on brain function and behavior. In one study, healthy women were randomly assigned to receive a fermented milk product probiotic (FMPP) containing a mix of *Bifidobacterium animalis* subsp. *Lactis, Streptococcus thermophilus, Lactobacillus bulgaricus*, and *Lactococcus lactis* subsp. *Lacti* in a placebo-controlled study.[90] The treated subjects then underwent emotional attention task testing and brain activity was measured using functional MRI analysis. A 4-week treatment with FMPP was associated with a significant change in the insula, periaqueductal gray, and somatosensory cortex regions compared with either no intervention or control-treated women, indicating that probiotic treatment in humans can result in modified brain activity. In another placebo-controlled study, healthy human

adults treated with *Bifidobacterium longum* 1714 had reduced stress and improved memory as measured by EEG changes during rapid information processing and cortisol levels.[4] These effects appear to be probiotic specific as *Lactobacillus casei* strain Shirota (LcS) relieved stress-associated symptoms in mouse and human models,[89] whereas *Lactobacillus rhamnosus* (JB-1) did not improve these measures.[48]

More importantly, mice with spinal cord injuries that were treated with VSL#3 (a commercially available probiotic) starting on the day of injury and lasting through 35-day postinjury demonstrated reduced neuropathology, improved locomotor recovery, and triggered a protective immune response through an increase in the number of Treg cells.[49] Similarly, a 10-day treatment with *L. bulgaricus* (10 trillion CFU/cp plus activated charcoal) was assessed in 64 patients aged 19–78 years old with severe TBI in a prospective, randomized, and placebo-controlled trial. Treatment with the probiotic was associated with a statistically significant decrease in diarrhea and length of stay in the ICU as compared to the control group. Another study also revealed that *L. bulgaricus* treatment led to a decrease in ventilator-associated pneumonia infection rate and duration of mechanical ventilation.[68]

CONCLUSION

SBI is an unavoidable outcome of all neurosurgeries and can potentially have long-term neurofunctional consequences for patients. Even with the development of minimally invasive procedures, neuronal tissue is damaged due to physical manipulation and this damage is often irreparable due to the nature of neuronal cells. Therefore, the only way to treat SBI is to limit the extent of injury while also preventing the progression of injury. There are a couple of therapeutics being investigated that may decrease the extent of SBI through activation of neuroprotective mechanisms or inhibition neuroinflammation.[79,94,98] These therapies involve the use of exogenous compounds that may have varying degrees of success based on absorption and ability to penetrate the BBB. One unexplored avenue for SBI prevention and limitation is the utilization and regulation of the MGBA. Unlike other therapies currently under investigation, treatment of dysbiosis has the potential to activate neuroprotective mechanisms while also inhibiting neuroinflammation.

Recent research reveals that treatment of dysbiosis with dietary modifications, prebiotics or probiotics, decreases disease progression and severity in patients with depression and anxiety. Therefore, treatment of dysbiosis before surgery may limit the extent of SBI intraoperative and prevent progression in the postoperative setting. In addition, treatment of dysbiosis through dietary modification, introduction of naturally occurring prebiotics or probiotics represents an easily accessible, more cost-effective option compared to the exogenous compounds such as Slit2 and MFGE8, currently being investigated.

The current evidence supporting the role of MBGA in limiting acute brain injuries is minimal. This is in part due to the fact that the majority of research has focused on the role of chronic dysbiosis in the development of chronic neurological diseases. However, investigations of dysbiosis treatment in acute brain injuries from trauma or surgery are promising and suggest a role of dysbiosis in acute neurological dysfunction. In one study, researchers showed that when mice were pretreated with GOS for 18 days, they had better cognitive recovery following abdominal surgery compared to controls.[99] In addition, in a 2004 study, researchers found that human brain injury patients had decreased length of stay in the ICU and length of mechanical ventilation when treated with probiotics.[33]

We recognize that there are many caveats to the evidence supporting the role of dysbiosis treatment and SBI presented in this paper. For one, most research has been conducted in animal models; therefore, the true impact on human health is not well understood. Second, the pathophysiology of SBI is not well understood and may vary between patients. In addition, we currently do not know which treatment methodology for dysbiosis is best or how much treatment is necessary or sufficient. Nevertheless, a therapy to limit and prevent the progression of SBI is greatly needed as SBI affects all 800,000 patients undergoing neurosurgical procedures each year. Treating dysbiosis with dietary modification, prebiotics, or probiotics to limit SBI may represent a cost-effective, non-harmful solution and deserves to be further explored.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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