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Review Article

Promising Role of Fecal Microbiota Transplantation in Stroke Management

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Abstract

Stroke, a cerebro-vascular disease presents a major global health problem, rated as the world's second-leading cause of death and the third most common cause of disability. Although in recent years there have been remarkable achievements in prevention, treatment, and recovery of post-stroke complications still, there is not a definite solution to overcome for this global problem. Differential transcription of certain gene segments are implicated in the location of stroke, which imbalances the proteome. Protein IL-1β anticipated to be the main culprit for the epigenetic modifications. Link between faecal microbiota transplantation (FMT) and Stroke management has been tried in rat model which gave promising results. In the recent past, several studies have indicated the key role of the gut microbiota composition and its alterations in the pathophysiology of stroke similar to many other diseases. In the present review, the alteration of gut microbiota due to the disease as well as dysbiosis of the microbiota as a causal factor for the development of the disease is discussed. The results of FMT trials in animal models and few human trials are summarised.

Keywords: Stroke; Gut-Brain axis; dysbiosis; risk factors; FMT

Introduction

Stroke, a cerebrovascular disease presents a major global health problem rated very high in terms of disability and death. Ischaemic stroke and hemorrhagic stroke are the two types, and ischaemic stroke accounts for 85% of all strokes. Neuronal damage due to stroke induces series of complex pathophysiological processes, including neuroinflammation, excitotoxicity, oxidative stress, and apoptosis. Ischaemic stroke caused by sudden occlusion of cerebral blood vessels resulting in cerebral hypoperfusion and neuronal damage. If left untreated promptly, ischaemic stroke will lead to serious consequences [1].

Certain gene segments are transcribed differently there, after the stroke, which imbalances the proteome. These epigenetic modifications occur most frequently in the heart, where they can cause scarring and impair pumping function. [2] identified that protein IL-1β is the main culprit for the epigenetic modifications which affect immunological memory after a stroke [2].

Although in recent years there have been remarkable achievements in prevention, treatment, and recovery of post-stroke complications till now, however, there is not a definite solution to overcome for this global problem [3],[4] in their systematic review to understand the link between Fecal microbiota transplantation (FMT) and Stroke management. FMT from healthy or ischemic donor to other ischemic recipient was found to affect brain infarct volume and survival rate, neurological and behavioural outcomes, and inflammatory pathways. In the recent past, several studies have indicated the key role of the gut microbiota composition and its alterations in the pathophysiology of stroke [4,5].

Microbiota-Gut-Brain Axis

However, evidence suggests that bidirectional communication exists between the gut and its microbiota and the brain designated as the microbiota-gut-brain axis. The initial dose of microbes from mother, multiply and the grown up human body contain in a range of 30 to 40 trillion in numbers. Among the many chemicals they produce, some are beneficial to the host and others are harmful. Hundreds of neuro-chemicals produced by the gut microbes after the gut-brain axis is established regulate basic physiological processes as well as mental processes such as learning, memory and mood. In turn the dysbiosis and inflammation of the gut are

responsible for anxiety and depression which are prevalent in society today [6].

Signalling between the brain and the gut occurs through both neuronal and non-neuronal mechanisms. The top-down signalling (brain→gut) from brain to gut wall is a direct communication via parasympathetic and sympathetic nerve fibers, or indirectly following stimulation of the enteric nervous system located in the submucosa and myenteric plexi of the gut wall. These neuronal signals influence gut motility, gut permeability, microbiota makeup, and resident immune cell activation.

Bottom-up signalling (gut→brain) is thought to occur through several different mechanisms. 1. The vagus nerve, composed of 80% afferent and 20% efferent fibres, serve a dual role in conveying signals between the gut and brain, stimulated by microbial compounds and metabolites as well as hormones (eg, serotonin, cholecystokinin, glucagon-like peptide-1, and peptide YY) released from enteroendocrine cells of the gut epithelial layer to initiate bottom-up signalling .

2. Immunogenic endotoxins from the microbiota, such as lipopolysacchride (LPS), has the capability to induce neuroinflammation either directly or via activation of peripheral immune cells which migrate to the brain.

3. The microbiota generate or stimulate the release of a number of metabolites, such as neurotransmitters, short-chain fatty acids (SCFAs,), indoles, and bile acids, which enter the systemic blood and travel to the brain to modulate the function of neurons, microglia, astrocytes, as well as blood-brain barrier (BBB). Microbiota of the gut is capable of producing neurotransmitters to have an influence on the host in addition to provide binding sites for neurotransmitters on bacteria that influence bacterial metabolism, proliferation, and virulence [5].

Risk factors and dysbiosis

Over the past decade, it has become apparent that the gut microbiota is very relevant to the development and progression of a number of neurological diseases including autism spectrum disorder, anxiety, depression, Alzheimer disease, Parkinson disease, vascular cognitive impairment, multiple sclerosis [7 - 12].

Earlier the link between hypertension as well as vascular dysfunction and FMThas been discussed elaborately [14]. Adnan et al. [14] performed in rat, FMT using caecal contents from spontaneously hypertensive stroke prone rats (SHRSP) and normotensive WKY rats. A significant increase in the Firmicutes: *Bacteroidetes* ratio in the hypertensive WKY g-SHRSP, as compared with the normotensive WKY g-WKY ($P = 0.042$) and they documented a strongevidence that presumably bacteria or bacterial products, were responsible for the induction of hypertension and concluded that gut dysbiosis can directly affect systolic blood pressure (SBP). A causal relationship exists between the gut microbiota and hypertension since, in a rat model of obstructive sleep apnea also induced hypertension. Mounting evidence strongly suggests a close relationship between gut dysbiosis and metabolic diseases such as Obesity, and Diabetes Mellitus [15-16].

Very early during 20th century, Elie Metchnikoff, a Nobel Laureate and pioneer in immunology, hypothesized that bacteria residing in the colon were instrumental in initiating many diseases, including neurodegenerative diseases associated with aging. According to his theory, aging is caused by toxic bacteria in the gut and that lactic acid could prolong life. He correlated that longevity of Bulgarian peasants to their yogurt consumption with Bulgarian bacteria (now called *Lactobacillus delbrueckii* subsp. *bulgaricus*) [17-18]. With aging, susceptiblity to the progressive functional decline of the gut resident microbiota due to breakdown of the gut epithelial barrier, loss of enteric neurons, and altered mucosal immune function results in excessive production of proinflammatory cytokines. As a result of concomitant changes in gastrointestinal physiology, aging is also associated with significant shifts in the makeup of the gut microbiota including decreased microbial richness, diversity and a decrease in bacteria with anti-inflammatory properties. The cumulative effect of these changes, the ability of older individuals to cope with antigenic, toxic, physical, and ischemic stress proves to be the risk factor for developing stroke [5]. Huang, et al., [19] performed pyrosequencing on the gut microbiota of 31 elderly patients suffering with Acute Cerebral Infarction and compared with healthy controls. The control group had *Blautia obeum* relatively in abundance while the presence of *Streptococcus infantis* and *Prevotella copri* were relatively higher in the patient group. Based on their reports *Blautia obeum* was negatively associated with white blood cell count and *Streptococcus infantis* was positively correlated with creatinine and lipoprotein, methane metabolism, lipopolysaccharide synthesis, bacterial secretion, and flagellar assembly of the gut microbiota in the patient group which was expressed differently than that of the controls from KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis [19-20] were able to come to a conclusion that aging alone may be the causal factor to produce gut dysbiosis from their experiments where they exchanged gut microbial communities between young (≈3 months) and aged mice (≈20 months). Having a young microbiota, regardless of mouse chronological age, decreased mortality, increased motor strength, enhanced locomotor function and anxiety during the course of recovery from proximal (middle cerebral artery occlusion (MCAO) [20-21]. demonstrated the same beneficial effect of a young microbiota on recovery occurs even when the FMTs were initiated 72 hours following proximal MCAO [21]. The presence of selected species of microbiota, during maturation of the inflammatory system is required for a fully functional immune system including that of resident immune cells in brain [22]. Overall, conclusions from the literature support the role of gut microbiota in influencing outcome after stroke. Depending on how the gut microbiota is manipulated, the outcome following a stroke can be either harmful or protective. These studies in laboratory animals bring hope for altering the microbiota to limit the damage and hasten recovery from stroke in humans [5].

Influence of stroke on gut microbiota

Stroke, the neurological disorder is also responsible for the alteration in the gut microbiota qualitatively as well as quantitatively. Following conclusions could be drawn from animal as well as human trials that stroke altered gut microbiota and decreased faecal acetic acid concentrations. Yamashiro et al [23] analyzed the faecal gut microbiota and faecal organic acids in a Japanese cohort of stroke and control subjects. Ischemic stroke altered the abundance of several genera and species independent of age, type 2 diabetes, and hypertension. Increased abundance of *Lactobacillus ruminis* positively correlated with markers of inflammation in stroke patients [23].

Patients suffering with stroke and transient ischemic attack had more opportunistic pathogens such as *Enterobacter, Megasphaera Oscillibacter* and *Desulfovibrio* and fewer commensal or beneficial genera including *Bacterioides, Prevotella* and *Faecalibacterium* thus altering gut microbiota [24] and Bacteria originating from the small intestine was observed to contribute to post stroke infection [25].

Influences of Gut Microbiota on Stroke Outcome

A healthy gut, harbours a microbiota which stabilizes the gut wall and maintains inflammation at bay proving to be protective. On the other hand inflammation in the gut leads to exacerbate injury and also prolong or impair recovery. An interesting observation is that the anti-inflammatory microbiome was observed to use antibiotics to reduce the species abundance and diversity, while the proinflammatory microbiome was found to be antibiotic resistant [26]. Review of literature clearly indicated that depending on how the gut microbiota is manipulated, the outcome following a stroke

can be either harmful or protective in animal models. Conclusions could be drawn that results of these studies in laboratory animals bring hope for altering the microbiota to limit the damage and hasten recovery from stroke in humans.

After the development of stroke, integrity of the BBB is an important consideration for brain protection because the tight junction proteins between endothelial cells are responsible for the prevention of paracellular diffusion and translocation of various molecules in the blood to the brain and its extracellular fluid. *Clostridium butyricum*, a butyrate producer, *Bacteroides thetaiotaomicron*, an acetate and propionate producer, or sodium butyrate into adult germ-free mice was found to enhance BBB integrity [27]. The protective effects *Clostridium butyricum* treatment was attributed to increased butyrate and reduced oxidative stress in brain [28].

In humans, antibiotic treatment at the onset of stroke reduced the incidence of post stroke infections but did not significantly decrease the rate of post stroke pneumonia, change mortality, or alter functional outcomes in stroke patients.

FMT to manage stroke outcome

Wei et al.[1] compared the bacterial population in 3 sets of rats namely a control donor group (without any intervention,), sham group (underwent only dissection of common carotid, external and internal carotid arteries , without middle cerebral artery occlusion (MCAO) and FMT, MCAO group (underwent MCAO and normal saline gavage), and MCAO+FMT group (underwent MCAO and FMT). The relative abundance of *Firmicutes* was decreased and *Bacteroidota* increased in the MCAO group suggesting the alteration of gut mocrobiota induced by stroke. Overall representation of bacterial profiles of rats are *Firmicutes, Bacteriodota,Lactobacillaceae, Prevotellaceae, Porphyro monadaceae, Lactobacillus, Prevotella,* unclassified-*Clostridiales*, unclassified-*Lachnospiraceae*, unclassified-*Porphyromonadaceae*. Stroke was found to induce alterations in the gut microbiota such as diversity of gut microbiota species and an increase in the *Bacteroidota* in addition to many specific stroke-induced changes at the genus level. The promising role of FMT was demonstrated in alleviating stroke-induced gut microbiota dysbiosis, reduce cerebellar infarct volume, and decrease Ferroptosis. Ferroptosis is an iron-dependent programmed cell death involving iron metabolism and lipid metabolism.These results suggest that stroke can cause changes in the gut microbiota and that FMT can restore the abundance of these microbiota. [1,29-30] showed that the abundance of *Firmicutes* decreased in rats after stroke, while that of *Proteobacteria* and *Bacteroidota* increased. Restoration of the gut microbiome using FMT as a tool could be anticipated to yield a promising therapeutic effects in stroke patients.

Conclusions

The impact of dysbiosis of the gut microbiota as a causal factor for the prognosis of stroke rely solely on studies conducted in laboratory animals and hardly be translated to the human disease state without human trials. In addition, dysbiosis or an unhealthy shift in the gut microbiota is likely not an alteration in one or a few bacterial species. The altered gut microbiome needs to be viewed as an ecological community acting together to affect the host in a beneficial or detrimental manner.

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