Review Article

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Research progress in the relationship between intestinal flora and cerebral stroke

Liang Yang-bin[1]; Guo Zhi-gang[2]; Sun Chang-qing[1]*

[1]Department of Neurosurgery, Baodi District, China.

[2]People's Hospital, Tianjin 301800, China.

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***Corresponding Author:** Sun Chang-qing, Department of Neurosurgery, Baodi District, China.
Email: husband88@163.com

Abstract

Cerebral stroke, also known as "stroke" and "cerebrovascular accident", is an acute cerebrovascular disease, including ischemic and hemorrhagic stroke. Cerebral stroke is the first cause of death and adult disability among Chinese residents [1], characterized by high incidence, high mortality, high disability and high recurrence [2]. Recent studies have found that intestinal flora may affect the occurrence and development of cerebral stroke through various channels such as nervous, neuroendocrine, and immune systems [3]. The immune and inflammatory responses of cerebral stroke patients continue to participate in the whole process of brain tissue injury and repair. As the largest immune system, the digestive tract plays an important role in regulating the immune function of the body [4]. Understanding the changes and interactions of intestinal flora in cerebral stroke patients, and using intestinal flora as a new therapeutic target may be a new direction for cerebral stroke treatment.

Effects of cerebral stroke on intestinal flora

Cerebral stroke causes diversity, proportion and metabolites of intestinal flora changed: The human gut is home to a large number and a wide variety of microbial populations, which are collectively referred to as intestinal flora. The intestinal flora can be divided into five categories, namely Proteobacteria, Bacteroideta, Firmicutes, actinobacteria and verrucobacteria, which are mutually interrestricted and interdependent.The ratio of firmicutes/Bacteroidetes is an important indicator of intestinal flora imbalance [5]. After cerebral stroke, most patients will have intestinal flora imbalance, even constipation, intestinal bleeding and other serious intestinal complications. Studies have found that the intestinal flora in cerebral stroke patients were changed, which was mainly manifested as a decrease in intestinal bacterial diversity, imbalance of bacterial flora, and a significant increase in pathogenic bacteria such as enterobacteria, enterococcus, bacteroides and other streptococci [6, 7]. At the same time, the metabolites of intestinal flora were also changed, mainly manifested as changes in the proportion and quantity of short-chain fatty acids (SCFAs)and the increase of trimethylamine N-oxide (TMAO) [8]. These changes promote the increase of intestinal permeability and intestinal mucosal damage, further aggravate the destruction of intestinal barrier and intestinal flora imbalance, even bacterial displacement, resulting in secondary infection of cerebral stroke finally [9].

Relationship between different brain lobe damage and intestinal flora changes: The concept of "microbiota - gut - brain axis" proposed in recent years can be used to explore the interaction mechanism between intestinal flora and brain. It is a bidirectional communication network, and different regulatory pathway acts on different brain lobes and neural transmission pathways. On the one hand, gastrointestinal movement is regulated by the brain. For example, electrical stimulation of different cerebral lobes in cats can enhance or inhibit the motility of different anatomical parts of the stomach [10]. Cerebral strock caused the gastrointestinal hemorrhage, mainly becused the bleeding positiong involved the autonomic nerve fibers from the anterior hypothalamus to the medulla oblongata. The stress ulcer can be directly affected by different cerebral lobe and the amount of bleeding [11]. In the brain, frontal lobe is in connection with autonomic nerve function and mental activity, the anterior part of the temporal lobe is involved in human emotions and mental activities. On the other hand, the gut microbiota regulates psychiatric disorders,such as digestion, mood were regulated gut microbiota through by the hypothalamic-pituitary-adrenal axis(HPA).It has been reported that anxiety and depression are highly co-occurring with functional gut disease, while always showing dysfunction of the HPA axis [12, 13]. There is evidence that gastrointestinal disorders have a high co-occurring rate with neurodegenerative diseases such as Alzheimer's disease (AD)and Parkinson's disease (PD), suggesting that the intestinal flora imbalance

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may affect the occurrence of neurological diseases [14, 15]. Abnormal aggregation of α-synuclein is the histopathological marker of PD. α-synuclein can diffuse from the intestinal wall and rise retrograde through the vagus nerve to neurons in the dorsal motor nucleus of the vagus nerve in the brain stem and reach the densifiable part of the substantia nigra medialis, resulting in degeneration of dopaminergic neurons [16]. Dopaminergic neurons in the substantia nigra transport dopamine to the striatum through the substantia nigra - striatum pathway and participate in motor regulation of the basal ganglia, thus causing symptoms of Parkinson's disease. The diagnostic criteria for AD include atrophy of the middle temporal gyrus. So, we speculated that microbiota - gut-brain axis was a bidirectional communication network, Intestinal Flora's changes are correlated with the damage of different brain lobes such as brain stem, basal ganglia, hypothalamus, pituitary, frontal and temporal lobes.

Effects of intestinal flora on the occurrence and development of cerebral stroke

Relationship between intestinal flora and cerebral stroke risk factors: Obesity, hypertension, diabetes, hyperlipidemia and atherosclerosis are important and controllable risk factors for cerebral stroke. Studies have found that the intestinal flora directly or indirectly affecting these risk factors through microbiota - gut - brain axis [3].

Intestinal flora and its metabolites leads to obesity through affecting the process of lipid metabolism. A large number of research results have confirmed this view. For example, there are researchers who predicted their adult body mass by measuring the difference of fecal microbial composition in volunteers' childhood [17], the body fat content of mice can be changed by transplanting intestinal flora [18]. Compared with normal people, the intestinal flora of obese people increased in gram positive Firmicutes and decreased in gram negative Bacteroides, in addition,the fewer Bacteroides, the fatter who was [19, 20]. There is no unified conclusion on the mechanism of intestinal flora cause obesity. At present, it is mainly believed that intestinal flora increases fatty acid metabolism and energy storage by affecting the digestion and absorption of sugars and lipids and inhibiting faster-induced adipokines, thus leading to obesity.

Hypertension can trigger cerebral stroke, and its severity is closely related to the prognosis of cerebral stroke [21, 22]. Intestinal flora's metabolites can affect blood pressure, including SCFAs, TMAO, bisulfate, etc. [23]. Animal and human experiments have shown that the diversity of intestinal flora in hypertension patients was significantly reduced, especially the amount and types of bacteria that produce SCFAs [24], these changes of intestinal flora were similar to cerebral stroke patients.

The level of blood glucose will affect the composition of intestinal flora, the changes of intestinal flora composition and metabolites will further aggravate diabetes through chronic inflammation and insulin resistance [25, 26]. The bacteria that can promote the occurrence of diabetes include Enterococcus, Serratia, Lactobacillus, Klebsiella, actinobacteria and Escherichia, etc., while the bacteria that have antagonistic effects on diabetes include bifidobacteria, Prevotella, Bacteroides, Rothella and verruciaceae [27, 28].

Hyperlipidemia and atherosclerosis are also important risk factors for cerebral stroke. Research has found that intestinal flora imbalance are closely related to abnormal lipid metabolism, and Deoxyribonucleic acid (DNA)of intestinal flora has been found in atherosclerotic plaques [29]. The intestinal flora of atherosclerotic is seriously unbalanced, and the introduction of pro-inflammatory intestinal flora can accelerate the progression of atherosclerosis, while using probiotics to maintain the balance of intestinal flora can alleviate atherosclerosis plaque [30].

Intestinal flora affects the prognosis of cerebral stroke: The imbalance of intestinal flora and bacterial displacement are very unfavorable to the prognosis of cerebral stroke. Using regulation of intestinal flora and its metabolites to treat cerebral stroke, there are three main research directions,currently. First, add probiotics. Using bifidobacterium combined with enteral nutrition support to treat patients with severe ischemic stroke,

the number of diarrhea and stool characteristics are better than those of patients with severe ischemic stroke only with enteral nutrition support,the levels ofinflammatory factors such as C-reflecting protein and interleukin-6 (IL-6)were also lower than those of the latter [31]. A meta-analysis showed that probiotics improved intestinal flora imbalance , reduced the incidence of lung, gastrointestinal and urinary tract infections , and shortened hospitalization and bed rest time in patients with ischemic stroke[32]. Second, antibiotic therapy. A Study has shown that the cerebral infarction size and mortality of the mice decreased from those of the normal group if the middle cerebral artery occlusion model was established after the experimental mice were pretreated with antibiotics [33]. Opposite, the outcome of experimental mice was significantly worsened if using broad-spectrum antibiotics broken the balance of intestinal flora [34]. Third,intestinal flora transplantation,that is, the functional bacteria from the stool of a healthy donor are transplanted into the patient's gut to restore the balance of the patient's intestinal flora and treating related diseases. Lee et al. [35] selected four SCFAs-producing bacteria (including bifidobacterium, Clostridium symbiotic, Faecalis prevoii and Lactobacillus fermenti) transplantated into the intestinal tract of ischemic stroke mice, then, the levels of SCFAs increased,the exercise ability ameliorated and the inflammation reduced in stroke mice.Benakis et al [36] found that the cerebral infarction area of the mice was reduced by 54%, and the sensorimotor function was relatively better after using intestinal flora transplantation to treat cerebral infarction mice. These evidences suggest that intestinal flora has a

energetically effect on cerebral stroke prognosis.

The interaction between cerebral stroke and intestinal flora mediated by immune system: This two-way interaction between the brain and intestinal flora has derived the concept of "gut-brain axis", the mechanism of which is mainly composed of three hypotheses:nervous, neuroendocrine and immune pathways [3, 37]. Currently, the immune pathway is widely recognized and widely studied. After stroke, the body is in a state of stress, which will activate the immune system in the body, mainly including two aspects:First, pro-inflammation occurs, such as Th1, Th17 and γδT cells, which often aggravate brain tissue injury [38]; The second is to inhibit the occurrence of inflammation, mainly because Treg cells inhibit the inflammatory response by secreting IL-10 [39]. In the early stage of stroke, the number of intestinal gamma-delta T cells increases and migrates to the pia of the brain to increase inflammation by secreting IL-17. In the middle and late stages of stroke, intestinal bacteria induce the production of Treg cells through their metabolites and inhibit the differentiation and migration of γδT cells [36]. One study found that after the feces of stroke mice were transplanted into germ-free mice, the number of Th1 and Th17 cells in these mice increased after cerebral infarction, and the size of cerebral infarction increased, suggesting the existence of an immune response controlled by intestinal flora in the body [40]. Winek et al. found that healthy intestinal flora can reduce the occurrence of inflammation, thus playing a protective role in the occurrence and development of stroke [41].

Summary

The factors that affect the occurrence and development of stroke are complex and diverse. In recent years, more and more attention has been paid to the interaction between stroke and intestinal flora, but its specific mechanism remains to be further studied. Due to the different attention of different studies on microflora, there is no uniform conclusion on the specific changes of intestinal microflora in different sites after stroke. Therefore, to further clarify the role of intestinal flora in the occurrence and development of stroke and its detailed mechanism, especially to explore the causal relationship between specific intestinal flora and stroke, so as to provide a theoretical basis for the prevention and treatment of stroke through clinical manipulation of intestinal flora.

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