Review

Study of brain-gut-microbiome axis for diagnosis and treatment of Parkinson's disease.

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by neuronal loss and dysfunction of dopaminergic neurons in the substantia nigra, Some studies have also found that it is characterized by gastrointestinal symptoms. The brain-gut-microbiome axis has a strong relationship with PD, and flora imbalance is also related to the occurrence of disease. Inflammatory damage and α-synuclein caused by flora imbalance can be retrograde transported to the central nervous system along the vagus nerve. Early diagnosis of PD can be made according to early gastrointestinal symptoms, changes of flora and biomarkers. In view of the changes of intestinal flora, the use of probiotics and antibiotics or fecal transplantation to change the intestinal microflora can provide a new method for the treatment of PD. Other methods can also be used, such as drug therapy or surgical treatment.

Keywords.

Brain-gut-microbiome axis, Parkinson's disease, Probiotic bacteria, Inflammation

Introduction.

Parkinson's disease (PD) is a neurodegenerative disease that mainly affects dopaminergic neurons in the nigra-striatal pathway, which is mainly characterized by dyskinesia. [1]The neuropathological sign of PD is that α-synuclein aggregates are widely found in the central and peripheral nervous system .[2] Another sign of PD is the accumulation of Lewy bodies can be found in various parts of the brain and body. These Louis bodies are round, dense, eosinophilic inclusion bodies composed of misfolded α-synuclein, ubiquitin, complement proteins and cytoplasmic structural proteins. [3] In addition to dyskinesia, Parkinson's disease also shows many gastrointestinal symptoms. Constipation is the most common autonomic nervous symptom in PD. It is reported that about 80% of PD patients develop constipation. [4] As a gastrointestinal inclusion, α-synuclein has been studied as a potential biomarker of PD. [5] Bidirectional brain-gut-microbiome axis interaction is considered to be related to the well-known pathogenesis of brain-intestinal diseases. [6] In recent years, the role of intestinal tract in the development of PD has become more and more important. A large number of reports have shown that the

brain-gut-microbiome axis is dysfunctional in PD, suggesting that it may be involved in the pathophysiology of the disease. [7] the microflora greatly regulates the function and homeostasis of the intestinal tract as well as human health outside the intestinal tract. [8] A better understanding of the brain-gut-microbiome axis interaction should bring new insights into the pathophysiology of PD and make an early diagnosis. [9]According to the changes of intestinal flora, using probiotics and antibiotics or fecal transplantation to change intestinal microflora can provide a new method for the treatment of PD. [10].

Etiology of Parkinson's disease.

There are many causes of Parkinson's disease, such as inflammation in the digestive tract, genetic factors, environmental toxicological factors, aging, diet, flora changes and other factors. The vagus nerve is thought to be most likely the transport pathway of α synuclein, and vagotomy has been observed to reduce the risk of PD in humans .[11] However some research results are skeptical. [12] in addition, partial resection of the mesenteric nerve innervating the distal colon also delayed the transmission of α-synuclein. This suggests that in addition to vagal innervation, other pathways may also contribute to the transmission of α-synuclein [13] Aging is the main risk factor for the development of PD, and delaying the aging process has a neuroprotective effect on PD in animal models. [2] Parkinson's disease is also associated with host genetics. Goodrich et al have shown that the microflora in twins is more similar than that in unrelated individuals. [14] There are also some cases of PD that are idiopathic and may be caused by exposure to environmental toxins. PD is related to pesticide, and exposure to environmental toxins increases the risk of PD. Hillburns et al found that intestinal bacteria responsible for the degradation of certain environmental toxins, such as atrazine and naphthalene, changed in PD patients compared with patients treated with PD drugs. [14] When the intestinal barrier is damaged, the defective intestinal barrier can associate intestinal bacteria with immune activation, resulting in systemic inflammation, thereby damaging the blood-brain barrier and promoting neuroinflammation. Finally, nerve injury and degenerative [15] Flora changes also play an important role in Parkinson's disease. The prevalence of *Prevotellaceae* in patients with Parkinson's disease is 77.6% lower than that in healthy controls. The relative abundance of Enterobacteriaceae was positively correlated with postural instability and gait difficulty. [16] Intestinal microbes can stimulate the intestinal nervous system and then transmit information to the central nervous system through the vagus nerve in the autonomic nervous system. [17] Diet reflects that celiac disease is a gastrointestinal disease induced by gluten and is related to the pathogenesis of PD. According to the results of a preliminary study, 2 of the 67 patients with celiac disease in the cohort reported symptoms of PD. When these patients changed their diet to a more gluten-free diet, their symptoms improved. [18]

Diagnosis.

Gastrointestinal symptoms such as constipation in most patients with

Parkinson's disease (PD) usually occur a few years before the onset of major motor symptoms. Lewy bodies have been detected in intestinal pathology of patients with PD, so α-synuclein (α-syn) has been used as a potential biomarker of precursor PD. [5] [19] It has been suggested that the changes of intestinal microflora related to intestinal inflammation may help to initiate the misfolding of α-syn, and the changes of intestinal microflora precede in the process of PD or occur in the process of PD. [9] Therefore, bacterial taxonomy may be a potential biomarker to identify possible risk factors for the development of PD. [3] In patients with PD, the abundance of *Prevotellaceae* family is decreased, while that of Enterobacteriaceae is higher. There is a negative correlation between the course of PD and the abundance of *Faecalibacterium*. [8] [9].

Treatment strategy.

Current treatments for PD either add / replace DA, or prevent DA breakdown, or prolong the role of levodopa to help control tremors. [10] Glucagon-like peptide-1 (GLP-1), an effective T2DM drug that has a positive effect on the brain-gut-microbiome axis, can provide effective treatment options for neurodegenerative diseases. Glucagon-like peptide-1Receptor agonists can exhibit neuroprotective and neurotrophic effects in a variety of model systems in vitro and in vivo. [20] Analysis of fecal samples from PD subjects revealed a higher level of Enterobacteriaceae bacteria, which was positively correlated with the degree of gait and postural instability, as well as a decrease in the abundance of the *Prevotellaceae* family. The use of probiotics may relieve complications and reduce intestinal permeability, microbial translocation and neuroinflammation in enteric nervous system. Restoring intestinal function by taking probiotics may lead to better levodopa adsorption and improved behavioral and cognitive abilities, which is a common symptom in patients with PD. [21] Compared with placebo, probiotic treatment reduced the score of the Motor Disorder Association-Unified Parkinson's Disease rating scale. [22] For intestinal flora, there are also methods such as the use of antibiotics and fecal microbiome transplantation (FMT). Antibiotics may affect the brain-gut-microbiome axis. For example, minocycline shows neuroprotective effects in MPTP animal models by crossing the blood-brain barrier and preventing the loss of dopamine. [23] A case report from China showed that FMT significantly reduced short-term (one week) lower limb tremor and constipation in patients with PD. [24] Supplementation of exogenous recombinant human brain-derived neurotrophic factor (BDNF) or compounds that increase BDNF levels may improve constipation, oxidative stress and clinical symptoms of PD. However, treatment of mice with the BDNF receptor antagonist AN121can reverse the ameliorative effect of BDNF. [25].

Conclusion.

The early stage of Parkinson's disease may occur in the gastrointestinal tract, and there are many causes of Parkinson's disease. the immune inflammatory response caused by changes in intestinal flora is recognized by most people. α-synuclein can be retrogradely

transported along the vagus nerve to the central nervous system. Gastrointestinal symptoms with intestinal flora changes can be used for early diagnosis of PD, and inflammatory markers can also be used for early diagnosis of PD. For the treatment of PD, antibiotics, probiotics and fecal microbiota transplantation can be used for intestinal flora, other drugs or surgical treatments can also be used.

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