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Research Progress of Early Non-motor Symptoms of Parkinson's Disease

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Abstract: *Parkinson's disease (PD) is a chronic central neurodegenerative disease with high morbidity, prevalence and disability rate.PD is generally divided into motor symptoms and non-motor symptoms, of which motor symptoms include myotonia, static tremor, slow movement and postural instability. Constipation, olfactory disorders, sleep disorders, anxiety, depression and cognitive disorders are the main manifestations of non-motor symptoms. At present, the research on the early non-motor symptoms of PD is relatively scattered. Now, the literature and data on the early non-motor symptoms of Parkinson's disease in recent years are summarized and discussed systematically, and some effective preventive measures are proposed in order to provide new ideas and methods for the follow-up clinical treatment.*

Keywords: *Parkinson's disease; Non-motor symptoms; Non-drug treatment*

1. Introduction

Parkinson's disease (PD), as a common central nervous system degenerative disease in the elderly, its basic pathological characteristics are the degeneration of dopamine (DA) neurons in the dense area of the substantia nigra with the formation of eosinophil inclusion bodies in the cytoplasm, namely Lewy bodies, leading to the destruction of the substantia striatum pathway and the reduction of DA content in the caudate nucleus and putamen[1], the incidence of general male is higher than that of female[2].Reportedly About 2 percent of the world's 10 million or so sufferers are affected by the disease.As early as before, the International Movement Disorders Association (MDS) has divided the onset of PD into three stages: preclinical, prodromal and clinical stage;Among them, the onset stage of preclinical and prodromal phases is called "non-motor symptom", and the clinical phase is called "motor symptom".The harm of these symptoms will not only produce psychological burden on the patient, affect the quality of life and daily work, but also bring heavy economic pressure to the patient's family and society.Current research on Parkinson's disease in Chinese and Western medicine, although most mainly focus on the clinical stage of PD, but in fact, the non-motor symptoms of PD have received more and more attention in recent years.Therefore, based on the actual condition of PD and the idea of "cure no disease" in traditional Chinese medicine, early intervention to alleviate the pathological process of PD should be very key.This article systematically expounds the related research on the early non-motor symptoms of Parkinson's disease.

2. Non-motor Symptoms

2.1 Autonomic Nervous Disorder

In patients with Parkinson's disease, gastrointestinal disorders are often accompanied by their whole life, among which constipation is the most common and one of the most prominent non-motor symptoms. In recent years, constipation has been particularly prominent in PD patients, with a morbidity of 27.10%-70.39%[3]. Different from common functional constipation, Parkinson's constipation often presents the characteristics of stubbornness, repetition, volatility and refractory, it not only lasts the longest, and some even earlier than the onset of motor symptoms more than 20 years[4]Therefore, it is considered as one of the early signs of the disease. There have been studies It is

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pointed out that the disease first appears in the enteric nervous system, and then transfers from the intestine to the brain, and then spreads retrograde through the vagus nerve to the substantia nigra densa in the midbrain, resulting in PD.Until now, most studies on the microbiota of PD have focused on intestinal bacteria, and indeed there is increasing evidence that bacterial ecological disorders may play an important role in the pathogenesis of PD[5].

2.2 Have Sensory Dysfunction

Anosmia has long been considered a signature prodromal symptom of degenerative diseases such as PD[6], about 50 to 90 percent of PD patients have this symptom. Therefore, it is generally used as a marker of early sensitivity in the preclinical stage of PD.Symptoms such as reduced or loss of olfactory function, paraphilia, and phantom smell are usually shown.However, the pathological mechanism of PD with anosmia is not fully understood, and certain pathological studies have been conducted It was found that there were lesions in both the olfactory center and the peripheral olfactory bulb.Olfactory brain functional areas mainly include the amygdala, anterior piriform area, parahippocampal gyrus, and orbitofrontal gyrus. The orbitofrontal gyrus and orbitofrontal gyrus are involved in the information transmission and processing integration of the cognitive system at the same time, so they have a very important influence on olfactory function.It is reported that[7]In some patients with anosmia without PD symptoms, about 7% of them eventually developed Parkinson's disease after 4 years of follow-up.Studies have found that due to the presence of lewy body pathological deposits in the neurons of the dorsal raphe nucleus in PD patients, it is speculated that the pathological changes may reduce the level of serotonin in olfactory pathways such as the olfactory bulb and entorhinal cortex of patients, thus leading to the exacerbation of olfactory disorders in patients.Also, there are studies pointing out Smoking can cause anosmia in non-Parkinson's disease patients, while the opposite effect is found in Parkinson's disease patients. It is speculated that it may be related to the cholinergic system related to the protection of smell by nicotine. However, there is insufficient evidence to support the improvement of anosmia with nicotine transdermal patches currently on the market.

2.3 Sleep Dysfunction

Sleep disorders occur in 60 to 90 percent of patients with Parkinson's disease[8]It is not only becoming one of the common non-motor symptoms of Parkinson's disease, but also significantly affects the quality of life of patients.Sleep disorders include insomnia, rapid eye movement (RBD) sleep behavior disorder, excessive daytime sleepiness (EDS), restless leg syndrome, circadian rhythm disorders, and kathisia. Among them, insomnia accounted for 20% ~ 80%, REM sleep behavior disorder accounted for 39% ~ 46%, daytime excessive sleepiness accounted for 20% ~60%, and restless leg syndrome accounted for 3% ~ 21.3%.RBD has the highest sensitivity to predict the occurrence of PD, and the rest are also possible risk factors for PD.

RBD is a kind of heteromorphic sleep, which refers to the complex movement of the muscle delay in REM sleep associated with dreams in patients with deep sleep at night. It not only has a serious impact on the quality of life of patients and their families, but also may be a risk factor for early dementia.RBD can occur either during the prodrome of Parkinson's disease, which progresses over a long period of time, or after the onset of motor symptoms of Parkinson's disease[9].Therefore, early identification and diagnosis of RBD is very important.Some studies have reported that the arrest of neurons in the locus coeruleus is a prerequisite for the emergence of REM sleep, and its degeneration can lead to sleep disorders[10] .In addition, the neural activities associated with PD patients with EDS involve multiple neurotransmitter circuits, such as dopaminergic, 5-hydroxytryptamergic, cholinergic and norepinephrineergic.It has been found that restless leg syndrome is more common in PD patients with EDS than in patients without EDS[11].In modern medicine, PD with sleep disorders are mainly caused by long-term treatment with anti-PD drugs, changes in central neurotransmitter and the patient's own mental factors. Often, patients with PD with sleep disorders are more prone to fatigue, anxiety, depression, cognitive decline and other conditions.

2.4 Cognitive Dysfunction

The clinical manifestation of cognitive dysfunction is initially the decline of thinking ability and inattention, and then there will be a series of symptoms such as language and memory dysfunction and low executive function.In the early stage of Parkinson's disease, due to the increasing age of patients, coupled with the fact that PD patients are often complicated by cardiovascular and cerebrovascular

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diseases and diabetes, the causes of its damage are more complicated, thus affecting its identification and diagnosis.Generally, the disease is divided into mild cognitive dysfunction of Parkinson's disease and dementia of Parkinson's disease. About 20 to 30 percent of PD patients have mild cognitive impairment, and 60 to 80 percent of PD patients can eventually progress to Parkinson's disease dementia[12], have a serious impact on patients' ability to live independently.It has been found that the development of the disease is most closely related to neuropathological changes (including protein misfolding, neuroinflammation, microglia and astrocyte changes) and neurochemical transmitter changes (including dopamine and acetylcholine)[13-14].A study of toxin induced PD in animals showed that changes in motor function of the cortico-basal ganglia pathway were closely related to changes in cognitive function, and equal damage was observed in motor and cognitive areas of the basal ganglia and cortex[15]. It can be seen that the cortico-basal ganglia circuit is a neural network connecting the subcortical structure with the cortex, which plays a crucial role in motor control and non-motor functions.

2.5 Anxiety Symptoms

Anxiety symptoms, as one of the early non-motor symptoms, usually appear before PD motor symptoms, and the patients with anxiety associated with PD account for 40% to 50% of PD patients, anxiety not only reduces the quality of life of PD patients, but also aggravates the movement disorders and cognitive performance of PD patients. A study found [16]that anxiety affected the 39 arkinson's disease survey scores decreased by 29.00%, indicating that Parkinson's disease anxiety had a greater impact on patients' cognitive level, disease progression, and quality of life.In one study, two different structural brain imaging analysis techniques were used to demonstrate that PD anxiety is associated with decreased volume of the left amygdala, and PD pathology is speculated to be the basis of amygdala atrophy and constitute a risk factor for the development of anxiety .Studies show [17]that in PD patients, for some patients, some symptoms of anxiety often occur only when the clinical symptoms are relieved.In addition, the anxiety of PD patients is also related to their own psychological factors. For example, women and young patients may be more prone to anxiety because they cannot accept the fact that they are suffering from the disease.

2.6 Depressive Symptoms

Studies show that 35 to 42 percent of people with Parkinson's disease develop depression[18], which affects the motor symptoms of PD and leads to the accelerated course of PD.However, in China, due to the lack of people's attention, the optimal period of treatment is often delayed, which can affect the cognitive ability of patients in serious cases, increase the risk of suicide, and bring unnecessary burden to the family and society. The study suggests that the occurrence of serotonin genotypic polymorphisms in depressive symptoms of patients with Parkinson's disease is of great significance, and the S/S allele is more prone to depressive symptoms[19].In addition, PD with depressive symptoms is often the result of dual or even multiple factors.On the one hand, the role of dopamine and norepinephrine is more important than that of serotonin;On the other hand, due to their own psychological factors, patients cannot accept the change of life ability and life status caused by PD, so it is easy to produce emotional disorders.

3. Summary and Outlook

At present, the incidence of non-motor symptoms of Parkinson's disease is high, and the pathogenesis is extremely complex. Generally, it is the result of the interaction of various factors, such as depression and cognitive decline will lead to the aggravation of the symptoms of apaxia.Cognitive disorders and sleep disorders may also further aggravate patients' depression.Therefore, early diagnosis and intervention are needed in clinical practice, so as to better predict the long-term development trend of PD, improve the prognosis of PD patients, and reduce the burden on families and society.

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