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Advances in the Study of Hyperhidrosis in Parkinson's Disease

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Abstract

Parkinson's disease hyperhidrosis is an important manifestation of Parkinson's autonomic dysfunction, which affects patients' quality of life and psychophysiological health to varying degrees, and it has received less attention compared with other autonomic dysfunctions. Currently, the main treatment for this disease is only based on local symptomatic treatment in Western medicine. Therefore, this paper summarizes the anatomical and pathological basis, mechanisms, and treatment options in recent years by analyzing the domestic and international literature on Parkinson's disease hyperhidrosis in recent years, in order to provide more references for clinical understanding of the treatment of Parkinson's disease hyperhidrosis.

Keywords

Parkinsonism; Tremor; Hyperhidrosis; Sweating Evidence; Autonomic Dysfunction.

1. Introduction

Parkinson Disease (PD), also known as tremor palsy, is a neurological disorder characterized by the degenerative death of dopaminergic neurons in the substantia nigra with the production and deposition of Lewy bodies as the main pathological changes, with the main clinical manifestations being motor and non-motor symptoms[1-2]. The main clinical manifestations are motor and non- motor symptoms.

Parkinson's disease was first reported clinically by James Parkinson in 1817, but the report was mostly directed to the motor symptoms of Parkinson's disease. It was not until 1893 that the British neurologist Gower described hyperhidrosis and thermoregulation in his book, Handbook of Diseases of the Nervous System[3] . The main symptoms of thermoregulatory disorders in Parkinson's disease are intolerance to heat and cold and impaired sweating[4-5] , with hyperhidrosis being the main clinical manifestation of thermoregulatory disorders. It has been shown that patients with Parkinson's hyperhidrosis have more severe sleep disturbances and higher anxiety and depression scores than patients without hyperhidrosis[6] .

This paper is based on domestic and international research progress of sweating disorder in Parkinson's disease, and composes and summarizes the analysis and discussion of the medical community in this regard in recent years, in order to be useful for clinical purposes.

2. Epidemiology

Sweating disorders are prevalent in Parkinson's disease, but account for the lowest percentage of studies of autonomic dysfunction in Parkinson's. Current medical research on the prevalence of sweating disorders in Parkinson's disease varies widely, which may be related to the insidious nature of the symptom and its intermittent onset.

Foreign studies have suggested that the prevalence of thermoregulatory disorders in Parkinson's disease varies from about 5.5% to 12.9% in the early stages and about 64% in the

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later stages as the disease progresses[7] . There is also a related study[8] in which the impact of non- motor symptoms on quality of life was studied in 411 foreign Parkinson's patients and found excessive sweating symptoms in about 30.4% of patients.

In China, when Song Wei[9] et al. expanded the sample size based on this study on 693 Chinese likewise, they found that the percentage of patients with Parkinson's hyperhidrosis symptoms in the corresponding sample was 27.4%. When Xu Xiaoqing[10] et al. used a cross- sectional study to count the frequency of different symptoms of autonomic impairment in Parkinson's disease, they showed that hyperhidrosis accounted for 57.6% of autonomic dysfunction in Parkinson's disease, second only to nocturia (85.3%) and constipation (77.5%)[11].Although studies on the prevalence of excessive sweating in Parkinson's vary widely at home and abroad, it is clear that the sweating disorder in Parkinson's is closely related to the progression of the disease. 26.9% and a 3-year incidence of 34.4%, providing an objective basis for this view.

3. Anatomical and pathological basis

Body temperature regulation depends on the close cooperation between peripheral thermoreceptors, mainly skin and mucosa, and central thermoreceptors, mainly hypothalamus, brainstem reticular formation and spinal cord. The temperature receptors located in the skin and mucous membranes can sense the temperature changes of internal organs, while the central temperature receptors located in the hypothalamus and brainstem reticular formation can directly sense the temperature changes of blood flowing through the brain and spinal fluid. The hypothalamus is the body's thermoregulatory center, which can directly sense local temperature changes in the blood and preoptic area, and is also responsible for integrating afferent signals from the periphery and the center and regulating the activity of skeletal muscle, sweat glands, endocrine glands, blood vessels, brown adipose tissue and other effectors through neural and humoral pathways to complete the regulation of skin heat production and dissipation[5,12] .

Different parts of the hypothalamus respond differently to stimulation. Heat-sensitive neurons and cold-sensitive neurons in the hypothalamic preoptic area (POA) are distributed in a ratio of 3:1. Stimulation of this area can increase heat production through excitation of sympathetic nerves and stimulation of sweat gland secretion. Excitation of the dorsal hypothalamic nucleus (DMP) increases heat production not only through skeletal muscle warts, but also by stimulating brown adipose tissue. Excitation of the medial preoptic area of the hypothalamus (MPO) can inhibit skeletal muscle shivering and brown adipose tissue thermogenesis; excitation of the median septalpallid nucleus of the medulla oblongata (rRPa) can stimulate sympathetic excitation, causing skin vasoconstriction and decreased heat dissipation. When the body is thermally stimulated, MPO thermosensitive neurons are activated, which stimulate sweat gland secretion to increase heat dissipation on the one hand, and downstream inhibit DMP and rRPa neuron activity to lower body temperature on the other hand[13,14] .

α-synuclein is the main component of Lewy vesicles, and studies have demonstrated that α-synuclein is deposited in the body before the onset of clinical symptoms in Parkinson's patients[15]. α-synuclein is neurotoxic and induces degenerative necrosis in dopaminergic neurons, while oxidative stress, mitochondrial dysfunction, and genetic mutations can also increase the chance of abnormal α-synuclein folding. The widespread neurodegeneration of α-synuclein leads to a decrease in central dopamine secretion, resulting in the loss of some antagonistic effects on cholinergic neurons relative to excitation, i.e., excessive heat production due to skeletal muscle tremors and excessive sweating due to overproduction of sweat glands [13,14,16] .

The peripheral thermoregulatory process is mainly governed by sympathetic nerves, which stimulate sweat secretion by excitatory cholinergic receptors and norepinephrine receptors.

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The sweat glands in the human body can be divided into large sweat glands and small sweat glands according to their physiological functions. The small sweat glands are located in the peripheral skin and are the main effectors of thermoregulation. Although the density of small sweat glands is greatest in the palms and toes, sweating at the extremities is activated by emotional responses and is not involved in thermoregulation [17] .

4. Western medical mechanism

The pathogenesis of sweating disorders in Parkinson's disease is currently unclear. Sweating disorders are associated with central and peripheral thermoregulatory mechanisms and the use of dopaminergic drugs. The impaired thermoregulation in Parkinson's patients is the result of a combination of hypothalamic thermoregulatory center involvement and peripheral autonomic nervous system damage, as well as the use of dopaminergic drugs[5] .

4.1. Impaired thermoregulatory center

Early in the disease, the hypothalamic thermoregulatory center and the deposition of vagal Lewy vesicles cause extensive neuronal degeneration, which on the one hand directly affect thermoregulation, and on the other hand, reduced dopaminergic production leads to a relative hyperactivity of cholinergic transmitters.

Pathological studies have demonstrated that alpha synuclein deposition in Parkinson's patients is not limited to the hypothalamus and higher autonomic centers such as the brainstem, but that preganglionic neurons as well as sympathetic nerve cells can be involved. As early as 1978, J. William Langston[18] et al. used Lewy bodies as a marker of neurodegeneration in the autopsies of 30 Parkinson's patients and found that Lewy bodies were found in all 13 individually identifiable hypothalamus without exception.

Ellen Gelpi[15] et al. found deposition of alpha synaptic nuclear protein in both the intermediate lateral cell columns of the spinal cord as well as in the cerebral cortex. All of the above studies provide substantial evidence for impaired thermoregulatory centers due to neuronal degeneration in Parkinson's disease .

4.2. Peripheral neuropathy

Later in the disease, α-synaptic protein deposition within peripheral autonomic nerves and damage to cutaneous nerves innervating blood vessels, erector spinae, and sweat glands cause cold/heat intolerance in the limbs and abnormal sweating, which have a common pathological basis with excessive sweating after stroke[19] . Ningshan Wang[20] et al. found α-synaptic nuclear protein deposition throughout the dermis of autonomic nerves in skin biopsies of 20 Parkinson's patients. In addition, the study found significant morphological changes in the sweating nerves of Parkinson's patients compared to controls.

Because of nerve damage in the sweating pathway in Parkinson's patients, excessive sweating in Parkinson's patients presents in a chronic fluctuating asymmetric pattern, mostly localized, usually involving the side of the limb with severe motor deficits[7] . Appenzeller[21] et al. in a study of autonomic function in 25 patients with Parkinson's syndrome found that excessive sweating in Parkinson's patients occurred mostly in the head and neck as well as the upper limbs, which is referred to as axial hyperhidrosis. Therefore, it is believed that localized hyperhidrosis in the head and neck region is a compensatory hyperhidrosis caused by the absence of sweating due to nerve damage in the sweating pathways of the rest of the body[22] . However, some scholars have integrated 50 studies and found that the occurrence of hyperhidrosis is not always accompanied by oligohidrosis[23] , so the principle of compensation alone is not sufficient to explain it.

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4.3. Drug effects

For Parkinson's patients, tricyclic antidepressants (TCAs) represented by promethazine, amitriptyline, and doxepin, selective 5-hydroxytryptamine reuptake inhibitors (SSRIs) represented by fluoxetine, paroxetine, and sertraline, 5-hydroxytryptamine and norepinephrine reuptake inhibitors (SNRIs) represented by duloxetine and venlafaxine, and cholinesterase inhibitors are the most common drugs with autonomic dysfunction as the main side effect. drugs are the most common drugs with autonomic dysfunction as the main side effect, thus inducing excessive sweating in patients[24] .

Back in 1998, tricyclic antidepressants were found to produce hyperhidrosis in about 14% of patients when clinical studies were conducted[25] . Lemke[26] found about a 43% (7/16) chance of hyperhidrosis in 16 depressed patients with idiopathic Parkinson's disease treated with reboxetine.

In addition, cholinesterase inhibitors, mainly represented by Enrichen, are commonly used clinically to improve cognitive impairment and dementia in Parkinson's patients. This class of drugs inhibits acetylcholine hydrolysis and therefore also causes excessive sweating[27] .

Table 1: Drugs that Commonly cause Hyperhidrosis

Drug Class	Representative drugs	Mechanism
Antidepressants - TCAs	Amitriptyline, Doxepin Promethazine, Clomipramine	Increases synaptic gap monoamine transmitter concentration and increases brain monoamine content Blocking cholinergic M, histamine H1, dopamine D2 and other receptors
Antidepressants-SSRIs	Citalopram, fluoxetine Paroxetine, Sertraline	Increase in 5-hydroxytryptamine concentration in synaptic gap
Antidepressants-selective norepinephrine reuptake inhibitors	Reboxetine, Tappetto	Increases norepinephrine concentration in the synaptic gap
Antidepressants - SNRIs	Duloxetine, venlafaxine	Increase the concentration of 5-hydroxytryptamine and norepinephrine in the synaptic gap
Cholinesterase inhibitors	Enrichen, Galanthamine	Inhibits cholinesterase activity and reduces acetylcholine hydrolysis

Notably, excessive sweating in Parkinson's patients is closely associated with the wear-off phenomenon, the switching phenomenon, and dyskinesia[28] . A related study[29] performed continuous sweat measurements in Parkinson's patients who had taken dopaminergic medication and found that patients who possessed the switching phase, especially those in the off phase, had a significant increase in sweating measured on both hands during the observation period, which provides an objective basis for this conclusion.

5. Treatment

5.1. Drug treatment

Western medical treatment is based on symptomatic management of the cause, and a review of the patient's medical history should be conducted regarding the timing of the onset of hyperhidrosis, the concentration of dopaminergic drug metabolism in the body, the drug

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relationship, and the type of hyperhidrosis to first consider optimizing the dopamine treatment regimen. For compensatory hyperhidrosis in the head, neck, and hemiplegia of patients with Parkinson's disease, it has been suggested that no specific treatment is required[30] . However, some related studies have concluded that hyperhidrosis in Parkinson's disease affects patients' quality of life and is associated with patients' anxiety and depressive states[31] . Treatments for hyperhidrosis include over-the-counter and prescription antiperspirants, oral anticholinergic drugs,monobotulinum toxin A, iontophoresis (the application of a mild electric current through water), and ablation or removal of sweat glands[32-33] .

The commonly used clinical antiperspirants are topical medications represented mainly by aluminum chloride, with over-the-counter concentrations of 10-15% and prescription drug concentrations of about 20-25%. Aluminum salts can inhibit sweating by blocking small sweat ducts through the formation of plugs by the precipitation process of metal ions and mucopolysaccharides. However, aluminum chloride can form hydrochloric acid in the process of use, which can cause local irritation. Thianthong[34] et al. found in a randomized controlled study of 20% aluminum chloride and 20% aluminum tetrachloride in the treatment of axillary hyperhidrosis that the therapeutic effects of both were comparable, but aluminum tetrachloride did not produce hydrochloric acid in the process of use and was safer and more reliable than aluminum chloride.

Anticholinergic drugs are often used to treat primary hyperhidrosis, but there is insufficient clinical evidence for the treatment of Parkinson's hyperhidrosis. Studies have shown that

oxybutynin, a systemic anticholinergic drug, was the first to be used for the treatment of hyperhidrosis, and although effective, side effects have been seen at effective doses[35] . Therefore, anticholinergic inhibitors of hyperhidrosis are now mostly used topically. Grononium tosylate as well as sophoronium bromide have been proven effective in foreign clinical trials[36-38] , but have not been approved for marketing in China.

Botulinum toxin (BONT) is the most toxic toxin known and is responsible for the cleavage of acetylcholine-released neuronal vesicle-associated proteins into the neuromuscular junction[39] , but there are no randomized controlled studies using BONT in the treatment of Parkinson's hyperhidrosis, nonetheless, local injections of BONT have become one of the mainstream treatments for patients with primary hyperhidrosis, for axillary hyperhidrosis has a Grade A (i.e., determined to be effective) recommendation[40] .

5.2. Non-pharmacological treatment

Deep thalamic stimulation (STN-DBS) is an important option for the treatment of advanced autonomic symptoms as well as fluctuations in motor symptoms in Parkinson's patients[41] .

Several studies have demonstrated a significant effect of STN-DBS in the treatment of Parkinson's hyperhidrosis and improvement of autonomic nerves. The mechanism may be that the stimulation directly modulates the basal ganglia-thalamo-cortical circuit, thus modulating the thalamus, lateral frontal lobe, and anterior cingulate gyrus, thus improving autonomic symptoms[42-44] . A clinical study by Bjerknes[43] et al. confirmed that continuous STN-DBS still had significant improvement in thermoregulation and hyperhidrosis symptoms 12 months after surgery. In addition, STN-DBS has also been shown to improve sleep disturbances in Parkinson's patients.

In addition, there are also clinical studies that confirm that acupuncture of the corresponding acupoints can reduce the incidence or degree of hyperhidrosis in PD. Prof. Han Jingxian[44] , based on the theory of Sanjiao qihua, acupuncture acupoints of Tanzhong, Zhongbei, and Qihai, together with Waiguan, Feosanli, Blood Sea, and Qianting, with a unique approach and angle of acupuncture, reduced the incidence of Parkinson's combined sweating by 16.3%. Chen Yiyi[45] et al. treated Parkinson's hyperhidrosis with the combination of Fuyao (tonic) and Hegu

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(diarrhea)points on the basis of conventional acupuncture and observed that the total effective rate was 96.4% in the treatment group and 72.4% in the control group, with a difference of $p < 0.01$ between the two groups, which was statistically significant. Compared with deep thalamic stimulation, the mechanism of acupuncture in treating hyperhidrosis in PD is not clear; therefore, acupuncture theory may provide a new entry point for studying hyperhidrosis in PD.

6. Summary

Hyperhidrosis is a clinically common category of autonomic dysfunction in Parkinson's patients that is affected by multiple effects of central and peripheral thermoregulation disorders as well as the effects of medications and has a nonspecific clinical presentation. Studies have demonstrated that hyperhidrosis is positively correlated with sleep disturbances and severe movement disorders and can be used as a simple clinical tool to identify autonomic dysfunction in early Parkinson's disease[6]. Although compared to other autonomic dysfunctions, PD hyperhidrosis has less impact on the human body, in terms of its prevalence, research is still lagging behind and there is great room for research. Therefore, this paper hopes to clarify the anatomical and pathological basis, mechanism and clinical treatment measures of PD hyperhidrosis to provide greater possibilities for clinical attention and subsequent research.

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