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Current Status of Research on Repetitive Transcranial Magnetic Stimulation for Parkinson's Disease

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Abstract: ***In recent years, repetitive transcranial magnetic stimulation (rTMS) for the treatment of Parkinson's disease (PD) has become a hot research topic both domestically and internationally, and has made many progress. Parkinson's disease is a degenerative disease of the nervous system, mainly caused by the loss of dopamine neurons and related motor and non motor symptoms. At present, drug treatment is still the main approach for Parkinson's disease, but long-term medication can lead to drug resistance and side effects, resulting in poor treatment outcomes. Therefore, it is necessary to explore new intervention measures. rTMS, as a painless and non-invasive brain stimulation therapy, has received increasing attention in the treatment of PD in recent years. The therapeutic effect and safety have also been widely recognized. This article reviews the current research status of rTMS on PD, aiming to provide reference for clinical treatment.***

Keywords: Repetitive transcranial magnetic stimulation, Parkinson's disease, Summarize**.**

1. Introduction

Parkinson's disease (PD), also known as “tremor paralysis”, is a common neurodegenerative disease that occurs in middle-aged and elderly people [1], and its clinical manifestations include motor symptoms (e.g., bradykinesia, resting tremor, and muscle rigidity) and non-motor symptoms (e.g., constipation, depression, cognitive impairment, and sleep disturbance) [2]. Currently, the number of Parkinson's patients worldwide is close to 10 million [3], and China has entered an aging society, with data showing that the prevalence of PD in people over 65 years of age in China is about 1.7% [4], and that the number of people suffering from Parkinson's disease will reach 5 million people by 2030, close to 50% of the global number of people suffering from PD [5].

Current treatments for Parkinson's disease are mainly medication and surgery. Levodopa (L-DOPA) is the most commonly used anti-Parkinson's disease medication in the clinic, but its efficacy decreases over the long term [6], and individual patients may experience poor control or intolerance of the medication, which makes the clinical symptoms of intermediate- to late-stage Parkinson's disease more complex and more difficult to treat. The efficacy of the surgery is certain, but there are corresponding risks. Therefore, in order to reduce the side effects of drugs on patients with Parkinson's disease, control clinical symptoms, and delay the disease process, we should also actively search for other adjunctive therapies in addition to drugs and surgical treatments [6]. Repetitive transcranial magnetic stimulation (rTMS) has been shown to be effective in improving several motor and non-motor symptoms of PD with few side effects, and it can significantly improve the quality of life of patients [2]. In order to gain a deeper understanding of the role of rTMS in the treatment of PD, this article reviews the current status of research on rTMS in the treatment of PD in recent years, with a view to providing a reference for the clinical treatment of Parkinson's disease.

2. Basic Understanding of PD

2.1 Etiology and Pathogenesis

There is no name for Parkinson's disease in Chinese medicine, but based on the clinical symptoms of involuntary tremors of the limbs and head, it can be categorized as “tremor syndrome”. The pathogenesis of fibrillation has been documented in ancient medical books, with internal and external causes, and the location of the disease is in the tendons, brain and marrow, as well as the liver, spleen and kidneys; the pathogenesis is complex and involves wind, fire, phlegm, and blood stasis. The liver is blamed in the early stages of the disease, and the disease is prolonged and injures the qi, blood, spleen and kidneys. 《Elementary Questions-Great Treatise on the Essentials of Supreme Truth》 was the first to state: “All windy diseases causing trembling and vertigo are related to the liver.” The liver governs the tendons, and the locus of disease is in the tendons and veins. “Sudden spasm and rigidity of muscles result from wind cold.” Liver belongs to wood, wood flourishes to generate wind, wind active, take the image to compare the tremor of the limbs belongs to the internal movement of the liver wind. The internal movement of liver wind is also used as the basic mechanism of the disease, and has become the source of the treatment of trembling syndrome for the later generations of medical practitioners. Hua Tuo also cited the liver as the main responsible organ, and the etiology of the disease was exogenous cold and heat. In the Ming Dynasty, Lou Ying blamed wind-heat, cold-dampness and phlegm for the cause of the disease. Sun Yikui suggests that this disease is more common in middle-aged and elderly people, and the root of the disease lies in the aging of the body, and the insufficiency of kidney yin, essence and blood.

Modern medical practitioners have inherited the explanations of the pathogenesis of tremor syndrome and the wisdom of ancient books from the sages of the past, and have further summarized the etiology and pathogenesis of tremor

syndrome by combining with what they have learned from their own clinics. Wang Yongyan [7], a master of national medicine, summarized his clinical experience and believed that the origin of fibrillation is in the deficiency and the mark is in the real, and the deficiency is in qi and blood deficiency and liver and kidney deficiency, and the real is phlegm-heat, stasis of blood and internal wind, and the disease is in the liver, and the spleen and kidney are injured in a long period of time. Zhou Shuping [8] believes that tremor is located in the brain, and the pathogenesis is closely related to the dong chi; because the dong chi has the function of supervising and leading the yang qi and the true essence, in addition, the dong chi has a close connection with the brain, the spinal cord, the kidneys, and the liver meridians, so the treatment should be to regulate the dong chi as the principle of acupuncture. Zhang Xiaoshan [9] pointed out that the pathomechanism of fibrillation syndrome is the deficiency of the root cause, the root cause is the deficiency of kidney essence, qi and blood, and the root cause is wind, fire, phlegm and blood stasis, and many factors are concurrently associated with the disease, so that both deficiencies and realities are often seen in the clinic.

2.2 Pathogenesis of PD

The currently recognized pathogenesis of PD is the loss of dopaminergic neurons in the dense part of the substantia nigra of the brain and the formation of Lewy's vesicles, which leads to the absence of dopamine in the patient's striatum and a relative increase in the action of acetylcholine, which causes disorders of the extrapyramidal system, leading to the development of non-motor and motor symptoms [10]. Non-motor symptoms include depression, constipation, cognitive impairment, and sleep disorders, and motor symptoms include bradykinesia, resting tremor, and muscle rigidity [11]. To this day, the pathogenesis of PD has not been fully explored, and as science continues to evolve, researchers continue to study the pathogenesis of PD. Braak, Heiko et al [12] categorized the pathological changes of PD into 5 stages based on the different locations where Lewy's vesicles appear: In stage I, Lewy vesicles appear at the olfactory bulb and the dorsal motor nucleus of the vagus nerve; in stage II, there are pathologic changes in the nuclei of the spinal cord and part of the nuclei of the pontine brain, affecting the brainstem, and patients will experience symptoms such as depression and insomnia; in stages III and IV, Lewy vesicles appear in the substantia nigra and telencephalon of the midbrain, and patients begin to experience typical motor symptoms, and PD is mostly diagnosed in this stage; in stages V and VI, the lesions affect the neocortex and the In stages V and VI, the lesion affects the neocortex and limbic system, and patients begin to show different degrees of neuropsychiatric symptoms, such as cognitive disorders, psychiatric abnormalities, dementia, depression and so on. Stages I and II belong to the preclinical period, when PD is often unnoticed; Stages III and IV are the clinical period, when motor symptoms appear, and it is easiest to diagnose PD; Stages V and VI are the late clinical period, when the damage to the cortex is more serious, and neuropsychiatric disorders will appear. The pathologic staging proposed by Braak, Heiko et al. provides a theoretical basis for the clinical development of PD.

3. Repetitive Transcranial Magnetic Stimulation

3.1 Mechanism of Action of rTMS

rTMS is a non-invasive brain stimulation technology, mainly through the pulsed magnetic field on the brain tissue, triggering the induction current, inducing nerve cell depolarization, and generating evoked potentials, so as to achieve the stimulation of neurons in the patient's cerebral cortex, regulating the function of the relevant parts of the cerebral cortex, and ultimately achieve the improvement of the clinical symptoms of Parkinson's disease patients [13]. It has been shown that rTMS can induce changes such as long-duration inhibition or long-duration enhancement by modulating cortical excitability [10]. It not only has transient effects such as modulation of neuronal membrane potential depolarization or hyperpolarization and intracellular ionic homeostasis, but also has long-lasting subsequent effects, including the production of long-lasting plasticity alterations, affecting neurotransmitter conduction and causing changes in the protein system of dopamine, γ-aminobutyric acid, and n-methyl-aspartate receptors within the neuron, which in turn can reshape synaptic function [14]. In addition, different frequencies have different effects on PD. Repetitive transcranial magnetic stimulation frequencies can be categorized into low (≤1Hz) and high (≥5Hz) frequencies, both of which can have sustained effects on cortical function. It is now generally accepted that low-frequency rTMS stimulation inhibits cortical excitability and decreases arousal, whereas high-frequency rTMS stimulation increases cortical excitability and increases arousal. Both low-frequency repetitive transcranial magnetic stimulation and high-frequency repetitive transcranial magnetic stimulation can have a positive effect on the symptoms of PD [2]. A related study by Xuehan Chen [15] concluded that high-frequency rTMS improves motor and nonmotor symptoms in PD patients.

3.2 Mechanisms of rTMS Action in PD

As a non-invasive brain stimulation therapy, rTMS has received increasing attention in the treatment of PD in recent years, and its efficacy and safety in PD have been generally recognized.

Repetitive transcranial magnetic stimulation was first applied to the treatment of Parkinson's disease in 1994, and its mechanism of action is as follows: by inducing the release of dopamine in the brain, promoting the synthesis of neurotrophic factors and regeneration of nerve fibers in the dopamine transport pathway, thus improving the clinical symptoms of Parkinson's disease [6]. Several studies have shown that repetitive transcranial magnetic stimulation can have an effect on Parkinson's disease in a variety of ways. rTMS can regulate a variety of inflammatory factors and play an antioxidant and anti-inflammatory role, thus protecting nerve cells; it can increase synaptic plasticity by increasing the synthesis and release of monoamine neurotransmitters, such as dopamine and 5-hydroxytryptophan (5-HT); and it can promote the expression of brain-derived neurotrophic factors, modulate the expression of neuronal genesis, survival, migration, and differentiation, and thus improve the function

and behavior of Parkinson's disease patients [2].

The Chinese Guidelines for the Treatment of Parkinson's Disease with rTMS published in 2021 [16], based on rTMS, made recommendations related to rTMS treatment protocols for motor symptoms with multiple non-motor symptoms in Parkinson's disease. Low-frequency (1Hz) rTMS stimulation of the primary motor cortex area of the brain is effective in improving gait impairment and postural deficits in Parkinson's disease patients [17]. High-frequency (10Hz or 5Hz) rTMS stimulation of the primary motor cortex area of the brain can improve the motor retardation of Parkinson's disease patients, and high-frequency (5Hz) or low-frequency (1Hz) rTMS stimulation of the bilateral motor areas of the brain can also effectively alleviate the motor symptoms of Parkinson's disease patients [18]. These studies have shown that rTMS is effective in improving motor symptoms in Parkinson's patients.

The Chinese Guidelines for the Treatment of Parkinson's Disease with rTMS state that the role of rTMS on overall cognitive function in PD has not yet been fully elucidated, and in our previous work we found that: High-frequency (5Hz) rTMS stimulation of the right parietal cortex of the brain improves learning, high-frequency (25Hz) rTMS stimulation of the inferior frontal gyrus improves frontal lobe cognition, and high-frequency (25Hz) rTMS stimulation of the dorsolateral region of the right prefrontal lobe of the brain improves executive and cognitive performance in Parkinson's disease patients [16]. Meanwhile, high-frequency (20Hz) rTMS stimulation of bilateral primary motor cortex areas of the brain can improve swallowing dysfunction in Parkinson's disease patients, while high-frequency (10Hz) rTMS stimulation of bilateral dorsal frontal lobe areas of the brain improves apathy in Parkinson's disease patients, and high-frequency (5Hz) rTMS stimulation of dingye or cortex in dorsal prefrontal lobe areas of the brain can improve the sleep quality in Parkinson's disease patients [16].

3.3 Adverse Effects of rTMS

Repeated transcranial magnetic stimulation may cause side effects such as dizziness, tinnitus, mild headache, and discomfort at the site of stimulation [19]. Of these side effects, headache and discomfort at the site of irritation are the most common, and symptoms are usually mild, short-lived, and most recover on their own [20]. The rTMS Safety Guide, 3rd edition [21] states that rTMS has very few side effects in psychiatric and neurological disorders. One of the most serious adverse effects is the induction of epilepsy, with a prevalence of between 0. 01% and 0. 10% [2]. Patients with Parkinson's disease tolerate rTMS well, and after adequate evaluation and monitoring. rTMS can be safely used in the majority of patients with Parkinson's disease [20].

4. Summary and Outlook

Repetitive Transcranial Magnetic Stimulation (rTMS) is a commonly used non-invasive neuromodulation technique in clinical practice. rTMS treatment has the advantage of being safer and more effective compared to surgical and pharmacological treatments for Parkinson's disease, and at the same time, it is easy to be accepted by patients, and it has been highly valued by the international and domestic medical communities [10]. And the existing clinical data of rTMS show that the method is safe and reliable with few side effects [22].

Currently, rTMS has become an indispensable and important tool for the study of neuroscience, and its efficacy in the treatment of PD has been recognized, but there are still many limitations: (1) The efficacy of rTMS varies from person to person, and therefore the therapeutic effect varies; (2) In the treatment and research of rTMS in Parkinson's disease, there are issues such as different stimulation intensities, different stimulation frequencies, and different target point selections, and there are no uniform efficacy standards for these parameters; (3) The mechanisms of action and target selection of rTMS for PD have not yet been fully elucidated, and some mechanisms may be too simple to be clinically effective in Parkinson's disease, as most of them are used only as theories. Therefore, future research should be done in the study: (1) Individualized treatment plans based on the patient's specific situation; (2) Conduct more clinical trials and studies to explore uniform, safe, and reasonable target selection, stimulation intensity, and stimulation frequency; (3) To further clarify the localization and mechanism of action of repetitive transcranial magnetic stimulation on cerebral brain areas, so as to provide a scientific basis for future precision medicine and clinical application. Looking forward to the broader application prospects of rTMS.

References

[1] Xie Renming, Li Yanru, Lei Da. Treatment of vascular Parkinson's syndrome after stroke by ultra-low frequency and high frequency repetitive transcranial magnetic stimulation [J]. Journal of Central South University. Medical Science, 2015, 40(4): 351-355.

[2] Nie Kun, Zhang Yuhu, Wang Lijuan. Research progress of neural regulation therapy for Parkinson disease[J]. Chinese Journal of Practical Internal Medicine, 2023, 43(10):831-838.

[3] Li J, Jin M, Wang L, et al. MDS clinical diagnostic criteria for Park inson's disease in China. J Neurol. 2017;264(3):476-481.

[4] Zhang ZX, Roman GC, Hong Z, et al. Parkinson's disease in China: prevalence in Beijing, Xian, and Shanghai. Lancet. 2005;365(9459):595-597.

[5] Parkinson's Disease and Movement Disorders Group of the Neurology Section of the Chinese Medical Association, Parkinson's Disease and Movement Disorders Group of the Neurologists Branch of the Chinese Physicians Association. China Parkinson's Disease Treatment Guidelines (Fourth Edition) [J]. Chinese Journal of Neurology, 2020, 53(12):973-986.

[6] Li Yuxia, Luo Zhenglong, Yin Lei, et al. Progress in Non-drug and Non-surgical Treatment of Parkinson's Disease[J]. International Journal of Geriatrics, 2023, 44(02):233-236.

[7] Wang Yongyan, Jiang Dashu, Hou Lina et al. Thirty-five cases of tremor paralysis syndrome treated with traditional Chinese medicine. [J]. Journal of Traditional Chinese Medicine, 1986, (08):22-24.

[8] Zhou Shuping. Light on the relationship between tremor-paralysis syndrome and the Duchenne vein[J]. Journal of New Chinese Medicine, 1997, (05):53-54.
[9] Zhang Xiaoshan. Treatment of Tremor Paralysis[J]. Journal of New Chinese Medicine, 1997, (06):61-62.
[10] Song Xiaodong, Wang Min, Su Qiang. Research progress of repetitive transcranial magnetic stimulation in the treatment of neurological diseases[J]. Journal of Shandong First Medical University & Shandong Academy of Medical Sciences, 2022, 43(08):635-641.
[11] Qiao Hongquan. The efficacy of low-frequency repetitive transcranial magnetic stimulation combined with pramipexole in the treatment of Parkinson's disease[J]. Journal of Medical Forum, 2020, 41(05):145-147.
[12] Braak Heiko, Ghebremedhin Estifanos, Rüb Udo, et al. Stages in the development of Parkinson's disease-related pathology. [J]. Cell and tissue research, 2004, 318(1): 121-134.
[13] Bao Huricha, Temuqile. Progress of Clinical Research on Sleep Disorders in Parkinson's Disease in Mongolian and Western Medicine. [J]. Journal of Medicine and Pharmacy of Chinese Minorities, 2023, 29(10):62-66.
[14] Zou Jianpeng, Bi Hongyan, Peng Wei. Application of non-invasive brain stimulation technique in rehabilitation of neurological diseases [J]. Chinese Journal of General Practice, 2017, 15(11):1948-1951.
[15] Chen Xuehan. Application value and effect analysis of high-frequency and low-frequency repetitive transcranial magnetic stimulation in Parkinson's disease [J]. Diabetes World, 2019, 16(4):118.
[16] Wang LiJuan, Nie Kun, Gao YuYuan, et al. Guidelines for repetitive transcranial magnetic stimulation therapy for Parkinson's disease in China[J]. Chinese Journal of Nervous and Mental Diseases, 2021, 47(10):577-585.
[17] Hamada Masashi, Ugawa Yoshikazu, Tsuji Sadatoshi, et al. High-frequency rTMS over the supplementary motor area for treatment of Parkinson's disease. [J]. Movement disorders: official journal of the Movement Disorder Society, 2008, 23(11):1524-1531.
[18] Wang LJ, Chen HB, Zhang YH. Evidence-based medical guidelines for the treatment of motor symptoms in middle- to late-stage Parkinson's disease in China[J]. Chinese Journal of Neuroimmunology and Neurology, 2021, 28(5):347-360.
[19] Qiu Yihui, Gao Yuyuan, Nie Kun, et al. Progress related to repetitive transcranial magnetic stimulation for depression in Parkinson's disease[J]. Chinese Journal of Neurology, 2018, 51(3):208-211.
[20] Shen Yao, Zhang Shushan. Progress of research related to repetitive transcranial magnetic stimulation for depression in Parkinson's disease[J]. Journal of Modern Medicine & Health, 2022, 38(11):1889-1892.
[21] Simone R, Andrea A, Sven B, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines[J]. Clinical Neurophysiology, 2020, 132(1).
[22] Zhu Xiquan, Duan Huifeng, Liang Xuejun. Research status of repetitive transcranial magnetic stimulation for the treatment of metabolic synd rome in schizoph renia patients[J]. Chinese Journal of Convalescent Medicine, 2024, 33(04):57-60.