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Application and Prospect of Repetitive Transcranial Magnetic Stimulation in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a common slow progressive dyskinesia disease in middle-aged and elderly people. In addition to typical motor symptoms such as ankylosis, bradykinesia and tremor, PD also shows non-motor symptoms (Non-motorSymptoms, NMS) such as depression, anxiety and cognitive impairment, which seriously affect the quality of life and physical and mental health of patients. In recent years, repetitive transcranial magnetic stimulation (rTMS), as a non-invasive brain stimulation technique, uses the principle of electromagnetic induction to produce magnetic field changes in the brain to induce current, stimulate the central or peripheral nerves, and cause nerve excitatory activity, thus effectively interfering with motor symptoms and non-motor symptoms of PD patients has been proved. This article reviews the application of transcranial magnetic stimulation in Parkinson's disease and expounds its mechanism so as to provide theoretical basis for clinical treatment.

Keywords

Repetitive Transcranial Magnetic Stimulation; Parkinson's Disease; Review.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease in middle-aged and elderly people. Progressive degeneration of dopaminergic neurons in substantia nigra and decreased dopamine secretion in striatum are significant manifestations of its pathological changes[1]. The morbidity, morbidity and mortality of PD increase with age. In China, the prevalence of PD in people over 65 years old is about 2.1% [2]. The clinical manifestations of PD include motor symptoms and non-motor symptoms [3]. The core of motor symptoms are motor retardation, rigidity and static tremor. Non-motor symptoms include dysphagia, depression, cognitive impairment, pain, anxiety, gastrointestinal dysfunction and so on. They are easily missed and misdiagnosed because of concealed onset and slow development, but non-motor symptoms affect the quality of life of patients as much as exercise symptoms throughout the whole course of the disease [4].

The pathogenesis of PD is complex, the clinical manifestations are diverse, and the treatment involves many dimensions, such as physiology, psychology, cognition and society. multidisciplinary comprehensive therapy is considered to be the best method for the treatment of PD [5]. The traditional treatment is dopamine replacement therapy and combined anticholinergic and other drug therapy, the deficiency of drug therapy is that the long-term treatment effect is limited, and the effect weakens with the passage of time, as well as the occurrence of toxic and side effects such as dyskinesia, obsessive-compulsive behavior, dementia and so on [6]. Exercise therapy and music therapy have also been proved to effectively improve the motor disorders of PD patients and improve their living standards [7], but the long treatment cycle, poor compliance of patients and the lack of professional

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therapists have become thorny problems that are difficult to promote in clinic. Repetitive transcranial magnetic stimulation (rTMS), as an alternative and innovative therapy, has exposed the head angle in patients with PD in recent years. A number of studies have also confirmed that different electromagnetic stimulation patterns in different brain regions can improve the symptoms related to Parkinson's disease in varying degrees [8].

2. Repetitive Transcranial Magnetic Stimulation

At the end of the 19th century, Barker et al found that the stimulation coil was placed in the cerebral cortex, and motor evoked potentials could be recorded in the corresponding limbs by electrical stimulation, so they proposed and established a method of using electromagnetic stimulation to treat nervous system diseases, that is, transcranial magnetic stimulation (TMS) therapy [9]. Transcranial magnetic stimulator is a kind of magnetic field which changes strongly from the energy storage capacitance to the stimulation coil based on the principle of electromagnetic induction. the magnetic field induces an electric current in the brain through the skull and stimulates the brain or peripheral nerves. Diagnosis and treatment equipment that produces a series of biological effects caused by nerve excitation. According to the different stimulation pulses, TMS can be divided into three stimulation modes: single-pulse TMS (sTMS), pulseTranscranialMagneticStimulation(pTMS), repetitive TMS (rTMS) and transcranial direct current stimulation (TDCS). RTMS is a kind of transcranial magnetic stimulation in the specific part of the cerebral cortex, which can be divided into high frequency and low frequency. High frequency (> 1Hz) can produce the sum of excitatory postsynaptic potentials, which leads to abnormal excitation of nerves at the stimulation site. On the contrary, low frequency (≤ 1Hz) is the inhibitory effect. The first rTMS instrument was produced in the United States in 1992, was approved by FDA in 2008 for the treatment of patients with depression, and expanded the use of rTMS in 2013. In China, in 2005, Huazhong University of Science and Technology developed China's first rTMS stimulator. With the continuous learning and innovation of domestic scholars in the direction of transcranial magnetic stimulation, the domestic rTMS technology level has been in the forefront of the world, and has been widely used in clinical departments, including neurology, psychology and so on, and has become an indispensable auxiliary means of clinical treatment.

3. Application of rTMS in Parkinson's Motor Symptoms

Ankylosis, bradykinesia and tremor are the most significant clinical manifestations in patients with PD, which is also the core of motor symptoms in patients with PD [10]. The results of a number of meta-studies at home and abroad suggest that rTMS may effectively improve the exercise signs of patients with Parkinson's disease in the short and long term [11]. The typical pathological changes of PD are dense dopaminergic deficiency in substantia nigra and decreased dopamine secretion in striatum, which are closely related to motor symptoms such as ankylosis, bradykinesia, tremor and so on [12]. There is a high correlation between the interaction and compensation mechanism between cerebellum activation and cortico-striatal motor loop dysfunction during exercise [13]. RTMS in M1 region of the brain can increase the release of dopamine in the putamen of patients with PD, thus effectively improving the motor symptoms of patients [14]. GiuseppeCosentino et al said that rTMS compensates for the reduction of factors related to subcortical dysfunction in patients with PD by enhancing cortical activity [15]. It is the most commonly used electrical stimulation mode to improve motor symptoms in patients with PD. HsiehTH intervened Parkinson's rats with rTMS intermittent θ burst stimulation mode, and confirmed that rTMS had neuroprotective effect and alleviated dyskinesia [16]. Although many pieces of evidence show that rTMS plays an auxiliary role in the treatment of Parkinson's disease, its efficacy and mechanism can not be clearly concluded because of its low statistical ability and other limiting factors. Large randomized placebo-controlled trials to assess the effects of rTMS on motor function and activities of daily living are still needed in the future to determine the long-term and short-term benefits of rTMS for Parkinson's disease.

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Clinically, patients with PD are mainly treated with compound levodopa. Compound levodopa is the most effective symptomatic drug in the treatment of motor symptoms of Parkinson's disease. However, long-term use of such drugs will inevitably lead to motor complications, including fluctuations in motor symptoms and dyskinesia [17]. Levodopa induced dyskinesia (LID) can be divided into peak dyskinesia, biphasic dyskinesia and terminal dyskinesia according to the relationship between clinical manifestations and medication time. Foreign scholars have studied the functional imaging of primary motor cortex (M1) and found that M1 is in a state of low activation in early untreated PD patients, while M1 is overactivated in patients with advanced PD treated with levodopa [18]. LID is closely related to the overactivation of M1 in PD patients. Low-frequency rTMS reduces the excitability of the target through the long-term depression-like effect of excitatory synapses [19]. This may be the reason behind the significant reduction of the severity of LID caused by low-frequency rTMS.

4. Application of rTMS in Parkinson's Motor Symptoms

4.1 Dysphagia in Parkinson's Disease

Dysphagia is a common NMS symptom of PD and a common clinical prodromal symptom. The incidence of dysphagia in PD patients is about 82% [20]. Dysphagia further leads to a high risk of malnutrition, social disorders, anxiety and depression, and aspiration pneumonia, and reduces the clinical and rehabilitation effects of PD treatment.

KoberSE et al. [21] by studying the swallowing process of real-time FMRI found that bilateral cerebellum, bilateral precentral gyrus, postcentral gyrus, basal ganglia, insular lobe, motor area, supplementary motor area (SMA) and other brain areas are active. Huang Peiling [22] et al. In a control study, 38 patients with PD were given high frequency rTMS of motor cortex once a day for 10 days. Functional magnetic resonance imaging (fMRI) was used to compare the changes of brain activation in PD patients with dysphagia and healthy controls. Compared with the control group, the activation of precentral gyrus, auxiliary motor area and cerebellum was enhanced in Parkinson's disease patients with dysphagia before treatment, and decreased after treatment. The activation of parahippocampal gyrus, caudate nucleus and left thalamus decreased before treatment, but increased after treatment. At the same time, the dysphagia index and the evaluation of swallowing efficacy suggested that the subjective swallowing sensation was improved. It is speculated that high-frequency rTMS can stimulate the release of neurotransmitters in the caudate nucleus of healthy people and patients with dysphagia of Parkinson's disease, thus enhance neuroplasticity [23]. By changing the release of neurotransmitters, it can promote the homeostasis of dopamine related to the caudate nucleus, and then improve the swallowing function.

4.2 Parkinson's Disease Depression

Depression is common in patients with PD and affects the progress of clinical treatment of the disease [24]. Neuropsychiatric disorders such as depression usually cause more trouble to patients and their families than the motor symptoms of Parkinson's disease. In addition to the inherent emotional disturbance, it can also have a serious negative impact on the quality of life, motor and cognitive impairment, dysfunction and other mental disorders of patients with PD.

The mechanism of depression in patients with PD is not clear, which is currently believed to be caused by the imbalance between the prefrontal cortex and the limbic system. Functional neuroimaging studies have shown that high-frequency rTMS in the left dorsolateral prefrontal cortex (DLPFC) may regulate abnormal cortical and subcortical activity in patients with depression in Parkinson's disease. The results of functional magnetic resonance imaging show that DLPFC has been considered as the standard target of high frequency rTMS in the treatment of Parkinson's disease. In 2016, Hae-WonShin et al. [25] through a randomized controlled trial, it was found that the scores of Hamilton rating scale, Montgomery-Asperger Depression scale and Baker Depression scale in patients with depression in Parkinson's disease were significantly improved from baseline to the 6th week after rTMS treatment in the left DLPFC area. It is proved that the high frequency rTMS of left DLPFC is

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a safe and effective method for the treatment of depression in patients with Parkinson's disease, and that the treatment of depression by rTMS does not affect the motor symptoms of Parkinson's disease during medication. Early studies have shown that tetrahydrobiopterin is a cofactor needed to promote the conversion of tryptophan and tyrosine, the precursor of monoamine, through phenylalanine hydroxylase (PAH) [26] . Tryptophan hydroxylase and tyrosine hydroxylase are necessary for the synthesis of neurotransmitters 5-hydroxytryptamine, dopamine and norepinephrine, all of which are regulatory disorders in patients with depression. Data from a clinical study conducted by the F.Leblhuber team [27] show that rTMS has an effect on PAH. PAH plays a key role in the biosynthesis of neurotransmitters dopamine, norepinephrine and epinephrine, all of which are downstream products of tyrosine. The reduction of tyrosine after the application of RTMS supports the possibility that this amino acid can be used to synthesize new neurotransmitters.

4.3 Cognitive Impairment of Parkinson's Disease

Cognitive impairment in patients with Parkinson's disease varies in severity, speed of progress and affected cognitive domain [28]; it ranges from mild cognitive impairment to mild cognitive impairment to dementia. Cognitive impairment in patients with Parkinson's disease increases the risk of turning into dementia.

The change of cortical excitability is a sign of cognitive impairment in Parkinson's disease. Studies have confirmed that the gradual excessive transmission of γ-aminobutyric acid, the deficiency of glutamate and the decrease of cholinergic transmission in the brain of patients with PD lead to the occurrence of dementia in Parkinson's disease. RTMS intervention significantly reduced the deterioration of PD-related symptoms [29]. EmanM.Khedr et al proved that high frequency rTMS in M1 region has a positive effect on cognitive impairment in patients with Parkinson's disease, but the effect is small, so it may be necessary to find more motor and frontal cortex regions as targets to apply rTMS [30]. High-frequency rTMS in the DLPFC region can also effectively delay the further deterioration of cognitive impairment in Parkinson's disease by enhancing the production of dopamine in areas such as the caudate nucleus [31]. In a controlled study by he Weijia et al, rTMS with intermittent theta burst stimulation achieved long-lasting and extensive therapeutic effects in patients with mild cognitive impairment in Parkinson's disease [32]. Overall, the evidence for the effectiveness of rTMS in the treatment of cognitive impairment in Parkinson's disease is still mixed and needs to be refined in the future.

4.4 Parkinson's Disease Pain

Pain is a non-motor symptom of Parkinson's disease that is easily overlooked. 40% of PD patients describe pain symptoms. Pain occurs at any stage of Parkinson's disease, even before diagnosis. At present, there is a lack of consistent classification system for Parkinson's pain. At present, five classification methods proposed by Ford et al are commonly used, which are musculoskeletal pain (MSP), nerve root / neuropathic pain, dystonia-related pain, agitation pain and central Parkinson's pain. Of these subtypes, MSP is the most common, with prevalence ranging from 40 to 90 per cent of PD patients who experience pain. Painkillers, opioids, antidepressants and anticonvulsants often can not relieve the pain of patients with Parkinson's disease. at present, dopaminergic and compound levodopa drugs are still in the best position for the treatment of Parkinson's disease pain. however, its limitations and side effects seriously perplexed patients [33].

The decrease of dopaminergic neurons in substantia nigra and the damage of substantia nigra-striatum pathway in patients with Parkinson's disease lead to the disturbance of pain regulation mechanism of dopamine, which is a possible mechanism leading to the decrease of pain threshold in patients with PD [34]. RTMS can achieve analgesic effect by stimulating the release of endogenous opioids and enhancing the secretion of brain-derived neurotrophic factor. The intervention of rTMS on pain in Parkinson's disease is mediated by a top-down regulatory mechanism. High-frequency rTMS stimulation of M1 area is an effective method for the treatment of pain syndrome, and the frequency of rTMS is mostly set to 10Hz and 20Hz [35]. However, the most exact target location of M1 stimulation has not been defined. In a randomized controlled double-blind trial, Li Jun et al confirmed

that high-frequency repetitive transcranial magnetic stimulation on the primary motor cortex may be an effective adjuvant therapy for relieving musculoskeletal pain in patients with Parkinson's disease . Zhu Yang et al found that low frequency (0.50Hz) rTMS on the basis of conventional drug therapy can also effectively relieve skeletal muscle pain and chronic pain in patients with PD.

4.5 Other

The non-motor symptoms of Parkinson's disease also include autonomic nervous dysfunction, constipation, hyperhidrosis, postural hypotension and so on. Low-frequency rTMS therapy interferes with autonomic nervous dysfunction in patients with Parkinson's disease by interfering with the expression of brain-derived neurotrophic factor and dopamine . There is a lack of experimental data on the direction of dysarthria in patients with Parkinson's disease. A systematic review indicates that rTMS can partially alleviate the symptoms of dysarthria in patients with Parkinson's disease, but there is still a lack of reliable and effective research results . For non-motor symptoms such as sleep disorders and anxiety, rTMS, as a non-invasive physiotherapy, can be effectively improved, and has the characteristics of safety and reliability, simple operation and less adverse reactions, so it provides an alternative adjuvant therapy for clinic.

5. Summary and Prospect

The incidence of PD in China is as high as 2.1%, and it is in a rising trend. The level of economic development in China still has a certain gap compared with that of western countries. The public's understanding of Parkinson's disease is still in the stage of motor symptoms. Non-motor symptoms have a certain degree of concealment and are easy to be ignored. At present, drug therapy is not only the best clinical treatment but also the most traditional treatment, but drug therapy has a modified effect on the movement and non-movement of Parkinson's disease, and has a certain degree of side effects. As a non-invasive and non-drug therapy, transcranial magnetic stimulation has a good therapeutic effect on motor symptoms and non-motor symptoms of Parkinson's disease through top-down regulation mechanism. RTMS mode can be changed according to the needs of patients. By adjusting parameters such as stimulation target area, frequency, mild stimulation, continuity and so on, the evaluation of curative effect mainly depends on patients' subjective feelings and scale scores, which is subjective, so it is difficult to form a unified standard of treatment. But generally speaking, as a "green" non-invasive treatment, rTMS is the direction of looking for a better treatment of PD.

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