THE EFFECT OF LOW-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ASSISTED DRUG IN TREATING FIRST-EPISODE SCHIZOPHRENIA AND ITS EFFECTS ON SERUM HOMOCYSTEINE, BRAIN DERIVED NEUROTROPHIC FACTOR AND COGNITIVE FUNCTION

Yi Lu[1,*], Jintong Liu[2], Dongdong Qiao[3], Guolin Mi[4], Guoqiang Ren[1], Wei Wang[5]
[1]Department of Physiotherapy, Shandong Mental Health Center, Jinan, PR China - [2]Department of Child and Adolescent Psychological Ward, Shandong Mental Health Center, Jinan, PR China - [3]Shandong Mental Health Center, Jinan, PR China - [4]Department of Ward Fifteen, Shandong Mental Health Center, Jinan, PR China - [5]Department of Ward Six, Shandong Mental Health Center, Jinan, PR China

ABSTRACT

Objectives*: To investigate the effect of low-frequency repetitive transcranial magnetic stimulation assisted drug therapy in treating first-episode schizophrenia and its effects on serum homocysteine (Hcy), brain-derived neurotrophic factor (BDNF), and cognitive function.*

Methods: *140 patients with schizophrenia admitted to our hospital between May 2018 and September 2019 were selected for comparative treatment. They were divided into treatment group (70 cases) and control group (70 cases) using the random number method. The patients were given oral risperidone for treatment, and the treatment group was given repetitive transcranial magnetic stimulation in addition to risperidone. Differences in the clinical efficacy, serum Hcy, BDNF, and cognitive function (i.e. memory, delayed memory, language function) of the two groups of schizophrenia patients were analysed.*

Results: *After treatment, the total effective rate was 94.28% in the treatment group and 81.42% in the control group, and the difference was statistically significant (P<0.05). The levels of Hcy in both groups were lower than before treatment, and the above indicators in the treatment group were significantly lower than those in the control group (P<0.05). After treatment, the levels of BDNF in the two groups were higher than before treatment, and the above indicators in the treatment group were significantly higher than those in the control group (P<0.05). The levels of memory, delayed memory, and language function in both groups were higher than before treatment; and the levels in the treatment group were significantly better than those in the control group (P<0.05).*

Conclusions: *Low-frequency repetitive transcranial magnetic stimulation combined with risperidone could improve the clinical efficacy of treatment, regulate the levels of Hcy and BDNF, and improve cognitive function such as memory, delayed memory, language function, etc., which is worthy of clinical application.*

Keywords: *Low-frequency repetitive transcranial magnetic stimulation, risperidone, first-episode schizophrenia, Hcy, BDNF, cognitive functions.*

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Introduction

Schizophrenia is a chronic severe psychiatric disorder, the cause of which is not clear, and it is clinically considered to be related to family genetic, environmental, psychological, and emotional changes. Typical symptoms are mental disorders, including victim delusions, jealousy delusions, and relationship delusions, among which the incidence of victim delusions is as high as 80%[(1)]. At present, many clinical drugs are used to treat schizophrenia. However, the use of drugs alone to treat schizophrenia has a lower total effective rate. Low-frequency repetitive transcranial magnetic stimulation (TMS) is a painless physical therapy for schizophrenia. It has been widely used in clinical practice, but there are few reports of low-frequency repetitive transcranial magnetic stimulation adjuvant drugs in the treatment of schizophrenia. Therefore, exploring low-frequency repetitive transcranial magnetic stimulation assisted drugs for the treatment of first-episode schizophrenia[(2)] has become a popular clinical

research topic. TMS has gained recognition for the clinical treatment of mental diseases by using magnetic signals to act on the cerebral nervous system, change the membrane potential of cortical nerve cells and improve brain metabolism and neural electrical activity in patients with mental illness[3]. Risperidone is an antipsychotic drug with a low affinity for beta receptors and toxic cholinergic receptors, which could effectively improve the positive and negative symptoms of schizophrenia[4].

Related studies have shown that homocysteine (Hcy) is neurotoxic. Increased cysteine levels are manifested by hypercysteinemia, which can accelerate aging, suppress immune function, produce cognitive dysfunction, and increase the incidence of dementia and schizophrenia[5]. Brain-derived neurotrophic factor (BDNF) can regulate neurotransmitters, increase synaptic plasticity, and promote nerve cell survival and neurogenesis[6]. Cognitive dysfunction can occur in patients with schizophrenia[7]. Therefore, in this paper, we explore the effect of low-frequency repetitive transcranial magnetic stimulation assisted drug therapy in treating first-episode schizophrenia, and its effects on serum Hcy, BDNF, and cognitive function.

Materials

Materials and methods

140 patients with schizophrenia admitted to our hospital between May 2018 and September 2019 were selected for comparative treatment. They were divided into a treatment group (70 cases) and a replacement group (70 cases).

The inclusion criteria were as follows:

• Patient condition complied with the schizophrenia-related diagnostic criteria indicated by the World Health Organization (WHO);

• Patient had a positive and negative syndrome scale (PANSS) score ≥60 points;

• Patients had no liver or kidney damage or other serious complications;

• Patients were aged 20 to 50 years old, no gender limit.

The exclusion criteria were as follows:

• Patients who had liver and kidney insufficiency and other complications;

• Women who were pregnant or lactating;

• Patients who were already taking antipsychotic drugs. The age of the treatment group was 20 to 50 years, with an average age of (26.54±4.56) years, the education period was 6 to 14 years, and the average education period was (8.65±1.56) years. The age of the control group was 20 to 49 years, the average age was (26.21±4.26) years, the education period was 7 to 14 years, and the average education period was (9.16±1.67) years. There was no significant difference in age or years of education between the two groups (P>0.05). This study was approved by the ethics committee of our hospital, and the patients and their families signed informed consent forms.

Methods

Patients in the control group were given oral risperidone (Belgian Janssen Pharmaceutical Co., Ltd., National Standard No.: H20161206, specifications: 1 mg, 10 tablets/plate, 2 plates/box). The starting dose on the first day was 1 mg, 2 times per day. On the second day, the dose was increased to 2 mg, 2 times per day. On the third day, the dose was increased to 3 mg, 2 times per day. The dose did not change after that, and the treatment was continued for 6 months. The treatment group was treated with low-frequency repetitive transcranial magnetic stimulation on the basis of the control group.

The KF-10 transcranial magnetic stimulator was manufactured by Shenzhen Kangli High-Tech Co., Ltd. A figure eight-shaped stimulation coil was used. The coil was parallel to the skull with the frequency set to 1 Hz, and the right lateral frontal dorsal region was selected as the stimulation site. The stimulus intensity started at the 50% threshold and gradually increased to 80%. Stimulation was sent to 1 to 2 wires per minute at intervals of 30 s. The treatment duration was 30 min per day, 5 d per week, ten times as a course of treatment, with two consecutive courses of treatment.

Observation indicators

The Positive and Negative Syndrome Scale (PANSS), which was used to determine the efficacy, improved ≥75%. The total effective rate was determined as (significant effect + effective) / total number of cases × 100%, where significant effect ≥60%, effective ≥25%, and ineffective <25%.

The content of serum Hcy was determined by the fluorescence polarization method. The instrument used the fully automatic chemiluminescence immunoassay technology of Abbott Corporation. Enzyme-linked sandwich immunosorbent assay was used to determine BDNF levels. Before and after treatment, 6 ml of venous blood was collected in the early morning when the two groups of patients were on an empty stomach. After 20 min of high-speed

centrifugation, the blood was stored at -20 °C. The kits were provided by Shanghai Beihai Fine Chemical Research Institute. According to the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the cognitive function level of patients (that is, memory, delayed memory, language function) was repeatedly measured.

Statistical methods

SPSS 22.0 software was used for statistical data analysis, and the measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$).

The t-test was used to compare the data of the treatment group with the control group, and the count data were represented by the rate (%). The χ^2 test was used to compare the data for the treatment group with that of the control group. P<0.05 was considered statistically significant.

Results

Clinical efficacy

After treatment, the total effective rate was 94.28% in the treatment group and 81.42% in the control group, and the difference was statistically significant (P<0.05). The results are shown in Table 1.

Groups	n	Significant effect n (%)	Effective n (%)	Ineffective n (%)	Total effective rate (%) n (%)
Treatment group	70	60 (85.71)	6 (8.57)	4 (5.71)	66 (94.28)
Control group	70	31 (44.28)	26 (37.14)	13 (18.57)	57 (81.42)
χ^2					5.423
p					0.019

Table 1: Comparison of clinical efficacy between two groups (%).

Serum Hcy levels in the two groups

Before treatment, there was no significant difference in Hcy levels between the treatment group and the control group (P>0.05). After treatment, the levels of Hcy in both groups were lower than before treatment; the above indicators in the treatment group were significantly lower than those in the control group, and the difference was statistically significant (P <0.05). The results are shown in Table 2.

BDNF levels in two groups

Before treatment, there was no significant difference in BDNF levels between the treatment group and the control group (P>0.05). The levels of BDNF in both groups after treatment were higher than before treatment; the above indicators in the treatment group were significantly higher than those in the control group, and the difference was statistically significant (P<0.05). The results are shown in Table 3.

Groups	n	Hcy (μg/L)		*t*	*p*
		Before treatment	After treatment		
Treatment group	70	21.56±4.61	12.45±2.67	14.307	< 0.001
Control group	70	21.23±4.37	16.38±2.97	8.473	< 0.001
t		0.434	8.233		
p		0.664	< 0.001		

Table 2: Serum Hcy levels in two groups ($\bar{x}\pm s$).

Groups	n	BDNF (μg/L)		*t*	*p*
		Before treatment	After treatment		
Treatment group	70	32.56±3.78	51.45±3.72	29.809	< 0.001
Control group	70	31.97±3.56	42.66±3.48	17.965	< 0.001
t		0.950	14.437		
p		0.343	< 0.001		

Table 3: BDNF levels in two groups ($\bar{x}\pm s$).

Cognitive function of two groups

Before treatment, there was no significant difference in the levels of memory, delayed memory, and language function between the treatment group and the control group (P>0.05). After treatment, the levels of memory, delayed memory, and language function in the two groups were higher than before treatment. The above indicators in the treatment group were significantly better than those in the control group, and the differences were statistically significant (P<0.05). The results are shown in Table 4.

Groups	n	Memory (score)		Delayed memory (score)		Language function (score)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Treatment group	70	62.45 ±3.28	83.87 ±3.71#	65.46 ±3.44	86.41 ±2.67#	79.13 ±3.45	89.61 ±3.58#
Control group	70	62.58 ±3.67	70.14 ±3.16#	65.98 ±3.24	72.43 ±3.41#	79.84 ±3.28	83.12 ±3.64#
t		0.221	23.571	0.920	27.006	1.247	10.635
p		0.825	< 0.001	0.358	< 0.001	0.214	< 0.001

Table 4: Cognitive function of two groups ($\bar{x}\pm s$).
Note: Compared with the same group before treatment, #P<0.05.

Discussion

Schizophrenia is a multifactorial psychiatric disorder. Clinical manifestations include sensory disturbances, mental disturbances, cognitive dysfunctions, etc. Sensory disturbances typically manifest as hallucinations, including hallucina-

tions, hallucinations, and hallucinations. The mental disturbances include obstacles in thought form and thought content, referring to obstacles in logic and continuity in the process of thought association, and thought obstacles such as victim delusion and relationship delusion. Patients with schizophrenia often deliberately have insecure cognitions such as surveillance and rejection, and patients with severe cases have aggressive behaviours[8].

Cognitive dysfunction refers to the lack of execution of patient information processing, instant memory, delayed memory, and so on. Related reports have shown that about 85% of patients with schizophrenia have reduced cognitive function, and those with significant form disorders and positive symptoms have more obvious cognitive deficits[9]. Low-frequency repetitive transcranial magnetic stimulation is an effective method for treating schizophrenia. Low-frequency repetitive transcranial magnetic stimulation is a non-invasive and painless physical therapy method for the cerebral cortex.

The electromagnetic field generated by the coil acts on the cerebral nervous system, which can improve the positive and negative symptoms of patients, as well as the physiological function and neural electrical activity of central neurons, stimulate patients' cognitive functions, and repair the cerebral cortex[10]. Low-frequency repetitive transcranial magnetic stimulation can also be used to assist the treatment of patients with mental symptoms such as depression and mania, and can effectively improve the clinical efficacy of patients[11]. Risperidone is a derivative of phenylprop isoxazole, which has a strong antagonistic effect on the 5-HT2 receptor and the dopamine D2 receptor. Risperidone can effectively improve the positive and negative symptoms of schizophrenia, and emotional symptoms such as depression and anxiety without significant anticholinergic adverse reactions[12]. The results of this study showed that the total effective rate of the treatment group was significantly higher than that of the control group, indicating that low-frequency repeated transcranial magnetic stimulation combined with risperidone could effectively improve the clinical efficacy of patients with schizophrenia.

Related research showed that Hcy is a sulphur-containing amino acid in the human body with neurotoxicity and is mainly eliminated by the metabolism of the kidneys. Increased Hcy levels are associated with genetics, nutritional status, and renal failure. The level of Hcy can reflect the body's health. If the level increases, this may result in hormonal problems, vascular and immune system diseases, brain function damage, cognitive dysfunction, and an increase in the incidence of Alzheimer's disease and schizophrenia[13].

BDNF is a neurotrophic factor synthesized by the brain that maintains the body's neurophysiological functions, regulates brain nerve functions, increases the body's antioxidant activity, and promotes the survival of nerve cells and neurogenesis. BDNF is a necessary nutrient factor for central and peripheral nervous system neurons to maintain physiological functions. Decreased BDNF levels can cause neuronal failure and increase the incidence of schizophrenia[14]. The results of this study showed that Hcy levels in the treatment group were significantly lower than those in the control group, and BDNF levels were significantly higher in the control group. This shows that low-frequency repetitive transcranial magnetic stimulation combined with risperidone can effectively improve Hcy and BDNF levels, improve protective factor levels, regulate the cerebral nervous system, and promote brain function recovery. Cognitive dysfunction in patients with schizophrenia continues to increase with the degree of cerebral cortical atrophy. Repeated low-frequency transcranial magnetic stimulation can effectively improve the excitability of the cerebral cortex, cerebral metabolism, cerebral blood flow, and improve the cognitive function of patients. Risperidone can effectively improve the positive and negative symptoms of patients[15]. The results of this study showed that after treatment, the levels of immediate memory, delayed memory, and language function in the treatment group were significantly higher than those in the control group. This suggests that low-frequency repetitive transcranial magnetic stimulation combined with risperidone can effectively improve patients' cognitive function and clinical symptoms.

In summary, low-frequency repetitive transcranial magnetic stimulation combined with risperidone can improve the clinical efficacy of patients, regulate the levels of Hcy and BDNF, and improve cognitive functions such as memory, delayed memory, and language function in patients, which is worthy of clinical application.

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Corresponding Author:
Yi Lu
Email: buuir0@163.com
(China)