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Effect of olanzapine combined with modified electroconvulsive therapy on cytokines, sTNFRs and neural electrophysiological characteristics in patients with schizophrenia

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ABSTRACT

Objective: To analyze the effect of olanzapine combined with modified electroconvulsive therapy on cytokines, sTNFRs and neural electrophysiological characteristics in patients with schizophrenia. **Methods:** Patients with schizophrenia treated in our hospital between March 2013 and March 2016 were selected and randomly divided into two groups, the observation group received olanzapine combined with modified electroconvulsive therapy, and the control group received olanzapine therapy. After 6 weeks of treatment, serum levels of soluble tumor necrosis factor receptor (sTNFR), acute phase reaction proteins and brain function indexes as well as the neural electrophysiological characteristics were compared between the two groups. **Results:** After 6 weeks of treatment, serum sTNFRs, CRP, CER and AAG content of observation group were lower than those of control group while TRF content was higher than that of control group; serum brain function indexes NGF and BDNF content were higher than those of control group while GFAP, S100B, NSE and Hcy content were lower than those of control group; nerve electrophysiology indexes P300, LPP and ERN amplitude were higher than those of control group while LPP amplitude was lower than that of control group. **Conclusions:** Olanzapine combined with modified electroconvulsive therapy can optimize the condition of schizophrenia, reduce the abnormal degree of nerve electrophysiology and help to improve treatment outcome.

1. Introduction

Schizophrenia is the clinical mental illness extremely hard to cure, it can involve perception, thought, emotion, behavior and several other aspects, and some patients may even develop cognitive dysfunction in the process of treatment[1]. Schizophrenia continues to progress in repeated attacks, the condition must be early controlled to prevent a series of long-term complications. Olanzapine is an atypical antipsychotic drug that can significantly improve the positive symptoms of patients with schizophrenia, but many studies have also found that the drug has little improving effect on the cognitive function in patients with schizophrenia[2]. Modified electroconvulsive therapy (MECT) belongs to physical treatment and is welcomed by clinicians for its efficiency, security and other features. Studies have shown that MECT can further optimize the schizophrenia condition and improve cognitive function, but there are still few such studies at home[3,4]. In the study, olanzapine combined with MECT was applied in the treatment of patients with schizophrenia in our hospital, and the levels of cytokines and sTNFRs as well as neural electrophysiological characteristics were specifically analyzed.

2. Materials and methods

2.1. General information

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A total of 102 patients with schizophrenia treated in our hospital between March 2013 and March 2016 were selected as the research subjects, and the inclusion criteria were: (1) in accordance with the WHO-established diagnostic criteria for schizophrenia; (2) with disease progression after 6 months of regular treatment; (3) patients signed informed consent; (4) with complete clinical data. Exclusion criteria were: (1) with congenital cerebral vascular anatomic abnormality; (2) with history of stroke; (3) associated with intracranial tumor diseases; (4) allergic to olanzapine and other drugs. The included patients were randomly divided into observation group and control group (n=51), control group included 26 male cases and 25 female cases, they were 18-53 years old and (36.83±7.91) years old in average, the course of disease was 1-7 years and (3.17±0.49) years in average; observation group included 27 male cases and 24 female cases, they were 17-56 years old and (35.91±7.86) years old in average, the course of disease was 1-8 years and (3.41±0.64) years in average. The two groups of patients showed no statistically significant difference in the distribution of gender, age and course of disease (P>0.05).

2.2. Treatment methods

Control patients received olanzapine therapy, specifically as follows: starting dose was 5 mg/d and increased to 10-15 mg/d within a week, and 6 weeks was as a course of treatment. Observation group received olanzapine combined with modified electroconvulsive therapy, specifically as follows: the patients took supine position, Scoline 1 mg/kg, etomidate 0.3 mg/kg and propofol 2 mg/kg were used for anesthesia, and after patients′ spontaneous breathing disappeared and limb tremor ended, the electrodes were placed in patients′ temporal side of dominant hemisphere, and the appropriate electric quantity was set. Determination resistance was less than 1 000 Ohms, electrode was electrified for 5 s, and after patients′ electroconvulsive shock was finished, valve airbag was used immediately for pressure oxygen supply and glucose liquid (25%) was intravenously dripped, focusing on the changes of patients′ vital signs during treatment. Treatment frequency: 3 times in the first week, 2 weeks a week from the second week, and 6 weeks was as a course of treatment. Olanzapine usage and dosage were the same as those of control group.

2.3. Observation indexes

2.3.1. Serum indexes

After 6 weeks of treatment, 2 mL of fasting peripheral venous blood was collected from two groups of patients, let stand at room temperature and centrifuged to get supernatant, and the specific detection indexes were as follows: (1) soluble tumor necrosis factor receptor (sTNFR): ELISA was used to determine sTNFR content; (2) acute phase reaction proteins: immune scatter turbidimetry was used to determine serum C-reactive protein (CRP), ceruloplasmin (CER), 1-acid glycoprotein (AAG) and transferrin (TRF) content; (3) brain function indexes: ELISA method was used to determine serum levels of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial fibrillary acidic protein (GFAP), S100B protein (S100B), neuron specific enolase (NSE) and homocysteine (Hcy).

2.3.2. Nerve electrophysiology detection

After 6 weeks of treatment, the state of nerve electrophysiology of two groups of patients was detected, and the concrete steps and parameter values were as follows: under the premise that patients were sober and relaxed, the recording electrodes were placed on the prefrontal area, central area and parietal area as well as superior border of left eye and right border of right eye, and Bravo brain evoked potential apparatus was used to measure P300, N250, late positive potential (LPP) and error-related negativity (ERN) amplitude.

2.4. Statistical methods

Data in the study was input in software SPSS23.0, measurement data comparison between two groups was performed by t test and P<0.05 indicated statistical significant differences.

3. Results

3.1. sTNFRs

Serum sTNFRs content of observation group of patients was (1 426.84±195.77) ng/L, serum sTNFRs content of control group of patients was (2 204.61±254.69) ng/L and serum sTNFRs content of observation group was significantly lower than that of control group (P<0.05).

3.2. Acute phase reaction proteins

Serum CRP, CER and AAG content of observation group were significantly lower than those of control group while TRF content was significantly higher than that of control group (P<0.05), shown in Table 1.

3.3. Brain function indexes

Serum NGF and BDNF content of observation group were significantly higher than those of control group while GFAP, S100B, NSE and Hcy content were significantly lower than those of control group (P<0.05), shown in Table 2.

3.4. Nerve electrophysiology indexes

P300, LPP and ERN amplitude of observation group were

Table 1
Comparison of acute phase reaction protein content in serum between two groups after treatment.

Groups	Case No.	CRP (mg/L)	CER (mg/L)	AAG (g/L)	TRF (g/L)
Observation group	51	3.74±0.41	284.62±30.17	0.69±0.07	2.76±0.31
Control group	51	5.98±0.63	342.88±40.36	0.85±0.09	2.45±0.29
t		6.823	11.039	5.212	5.483
P		<0.05	<0.05	<0.05	<0.05

Table 2
Comparison of brain function index content in serum between two groups after treatment.

Groups	Case No.	NGF (ng/L)	BDNF (ng/L)	GFAP (ng/L)	S100B (μg/L)	NSE (μg/L)	Hcy (μmol/L)
Observation group	51	39.46±4.52	32.84±4.09	19.74±1.83	0.18±0.02	7.12±0.89	12.18±1.76
Control group	51	26.77±3.45	21.64±2.58	26.53±2.91	0.27±0.03	18.43±2.17	18.95±2.64
t		7.381	9.283	8.342	5.192	8.934	7.263
P		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

significantly higher than those of control group while LPP amplitude was significantly lower than that of control group (P<0.05), shown in Table 3.

Table 3
Comparison of nerve electrophysiology index amplitude between two groups after treatment (mV).

Groups	Case No.	P300	N250	LPP	ERN
Observation group	51	5.38±0.61	8.29±0.95	5.38±0.63	9.12±0.95
Control group	51	3.72±0.41	7.11±0.84	8.91±0.95	7.05±0.82
t		5.934	6.012	7.384	7.483
P		<0.05	<0.05	<0.05	<0.05

4. Discussion

Patients with poorly controlled schizophrenia can show early recurrence of disease and aggravation of illness, and some patients may even develop irreversible nerve and important viscera dysfunction. Olanzapine exerts antipsychotic effect through the antagonizing 5-hydroxytryptamine, dopamine and other neurotransmitters to, it is the current clinical first-line drug to treat schizophrenia, but its role in optimizing patients′ cognitive function is limited, and other treatments need to be combined to enhance the overall curative effect[5]. MECT is a brand new physical treatment technology improved from the traditional electroconvulsive shock technology, which stimulates patients′ cerebral cortex through proper current, makes the electrical activities of the central nervous system synchronized, and realizes the purpose of disease treatment during the brief loss of consciousness in patients[6,7]. Domestic application of MECT is still in its infancy stage, and olanzapine combined with MECT was used in the treatment of patients with schizophrenia in our hospital in the study, and was specifically studied from the sTNFRs, cytokines, neural electrophysiological characteristics and other aspects.

sTNFR is the tumor necrosis factor receptor fragment hydrolyzed from cell membrane, it is the newly discovered factor closely related to schizophrenia, and research has found that sTNFR is highly expressed in Chinese patients and positively correlated with the severity of patients' positive symptoms. TNF-α can sensitively reflect the body's inflammation state, and high levels of sTNFR may also be related to the persistent and active inflammation in the brain of in patients with schizophrenia[8]. In the study, serum sTNFR content of two groups of patients were examined at first, and it was found serum sTNFRs content of observation group was lower after treatment, indicating that after added in the treatment, MECT has exact effect on the optimization of patients′ overall condition. Acute phase proteins are a class of proteins released by the body under the stimuli such as inflammation and infection, and studies have shown that there is increased content of the positive acute phase proteins and decreased content of the negative acute phase proteins in patients with schizophrenia, which further illustrate the important role of the inflammatory response in the occurrence and development of schizophrenia[9,10]. It was found in the study that CRP, CER and AAG content in serum of observation group were lower while TRF content was higher after treatment. CRP, CER and AAG belong to positive acute phase proteins, TRF belongs to the negative phase protein, and the above results are consistent with those described in many literatures and illustrate that MECT can reduce the inflammation state so as to optimize the condition of schizophrenia.

Cognitive function in patients with schizophrenia is also directly related to nerve cell damage, NGF, BDNF, GFAP, S100B, NSE and Hcy are all currently commonly reported factors directly related to neural function, and detecting the changes in contents of the above factors can intuitively reflect the cognitive status of the patients with schizophrenia. NGF can both nourish neurons and promote the growth of axons, and BDNF can repair neurons and ease neuron stress reaction. The structural integrity of astrocytes is very important to brain function, and abnormal GFAP expression can lead to the synaptic dysfunction, which is one of the important mechanisms of brain dysfunction in patients with schizophrenia[11,12]. Both S100B and NSE mainly exist within cells, and there is increased blood-brain barrier permeability in patients with schizophrenia, which leads to the release of S100B and NSE into the blood circulation[13]. Hcy is an independent risk factor for schizophrenia, and the continuously increased Hcy levels may even directly worsen the condition of

schizophrenia[14]. In the study, serum NGF and BDNF content of observation group were higher while GFAP, S100B, NSE and Hcy content were lower after treatment, indicating that MECT can optimize the neural function in patients with schizophrenia and further confirming that the exact effect of the therapy on optimizing patients′ cognitive function.

When receiving emotional stimuli, the people will produce the corresponding emotions and trigger the changes of electrical activities, and there are abnormal electrical activities of brain in patients with schizophrenia, including the changes of amplitude and latency, *etc*., and they can become the objective evidence of disease development[15]. P300 is the positive complex associated with psychological factors, and P300 amplitude decreases significantly in the violent people. Study has found that N250 peak appears relatively late and the amplitude is lower in patients with schizophrenia, which are associated with the impaired frontal lobe[16]. LPP is a kind of prolonged positive potential closely related to the emotional regulation and patients′ mental status, and LPP amplitude rises to different extent in patients with mental disorders. ERN amplitude is lower in the patients with schizophrenia, speculated to be associated with inhibition of nervous impulses. In the study, nerve electrophysiology of two groups of patients were detected, and it was found that P300, LPP and ERN amplitude of observation group were higher while LPP amplitude was lower after treatment, explaining that MECT can optimize the state of nerve electrophysiology in patients with schizophrenia, and is direct evidence of improved condition and optimized cognitive function in patients.

To sum up, it is concluded as follows: olanzapine combined with modified electroconvulsive therapy can optimize the condition of schizophrenia, reduce the abnormal degree of nerve electrophysiology and help to improve treatment outcome.

References

[1] Ratajczak P, Kus K, Giermaziak W, et al. The influence of aripiprazole and olanzapine on the anxiolytic-like effect observed in prenatally stressed rats (animal model of schizophrenia) exposed to the ethyl alcohol. *Pharmacol Rep* 2016; **68**(2): 415-422.

[2] Yu Q, Wang J, Chen H, et al. Olanzapine combined with modified electroconvulsive therapy for 94 cases of schizophrenia. *Herald Med* 2015; **34**(10): 1298-1301.

[3] Krakowski MI, DeSanctis P, Foxe JJ, et al. Disturbances in response inhibition and emotional processing as potential pathways to violence inschizophrenia: a high-density event-related potential study. *Schizophr Bull* 2016; **42**(4): 963-974.

[4] Chen LY, Chen Z, Li XJ. Serum cytokine contents in schizophrenia patient with metabolic syndrome and their correlation with nerve electrophysiology. *J Hainan Med Univ* 2016, **22**(13): 1422-1425.

[5] Kolomeets NS, Vostrikov VM, Uranova NA. The effects of blood serum fromschizophrenia patients under olanzapine monotherapy on the ultrastructure of astrocytes in human fetal brain organotypic culture. *Zh Nevrol PsikhiatrIm S SKorsakova* 2016; **116**(5): 65-70.

[6] Li X, Wang JJ, Xie B. Violence-related emotional regulation disorder and its brain electrophysiological mechanism in patients with schizophrenia. *J Psych* 2015; **28**(3): 225-228.

[7] Papaleo F, Yang F, Paterson C, et al. Behavioral, neurophysiological, and synaptic impairment in a transgenic neuregulin1 (NRG1-IV) murine schizophrenia model. *J Neurosci* 2016; **36**(17): 4859-4875.

[8] Šaki M, Karlovi D, Vidrih B, et al. Increased calcium-independent lipoprotein phospholipase A2 but not protein S100 in patients with schizophrenia. *Psychiatr Danub* 2016; **28**(1): 45-50.

[9] Vachev TI, Stoyanova VK, Ivanov HY, et al. Investigation of fasciculation and elongation protein ζ-1 (FEZ1) in peripheral blood reveals differences in gene expression in patients with schizophrenia. *Balkan J Med Genet* 2015; **18**(1): 31-38.

[10] Hamazaki K, Maekawa M, Toyota T, et al. Fatty acid composition and fatty acid binding protein expression in the postmortem frontal cortex of patients with schizophrenia: A case-control study. *Schizophr Res* 2016; **171**(1-3): 225-232.

[11] Niu LL, Wen KQ, Xiong P, et al. Correlation between pre-and post-treatment serum levels of NGF, BDNF, GFAP and severity of clinical symptoms in patients with first-episode schizophrenia. *J Psych* 2015; **28**(1): 10-13.

[12] Wen XY, Wang YH, Deng AP. Clinical significance of homocysteine and neuron specific alcohol in patients with first episode schizophrenia. *J Qiqihar Univ Med* 2016; **37**(8): 1045-1048.

[13] Dutta M, Nath K, Baruah A, et al. A clinical study of neurological soft signs in patients with schizophrenia. *J Neurosci Rural Pract* 2016; **7**(3): 393-399.

[14] Chan RC, Xie W, Geng FL, et al. Clinical utility and lifespan profiling of neurological soft signs in schizophrenia spectrum disorders. *Schizophr Bull* 2016; **42**(3): 560-570.

[15] Edgar JC, Fisk CL 4th, Liu S, RT, et al. Translating Adult electrophysiology findings to younger patient populations: difficulty measuring 40-Hz auditory steady-state responses in typically developing children and children with autism spectrum disorder. *Dev Neurosci* 2016; **38**(1): 1-14.

[16] Micoulaud Franchi JA, Quiles C, Belzeaux R, et al. Negative symptoms of schizophrenia: from electrophysiology to electrotherapy. *Encephale* 2015; **41**(6 Suppl 1): 6S50-6S56.