

Effects of the modified electric convulsive treatment (MECT) on cell factors of schizophrenia

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Abstract. The expression of cell factors of schizophrenia and the effect of the modified electric convulsive treatment (MECT) were studied. In total, 156 patients with schizophrenia were selected, and divided into the drug group (70 cases) and the drug combined with MECT group (combined group) (86 cases) according to the treatment methods. In addition, 70 cases of healthy volunteers (control group) were selected according to the closest matching method based on 1:1 of age and gender. The drug treatment, consisted of anti-psychotic drugs, such as risperidone 2-8, quetiapine 300-750, ziprasidone 80-160 or aripiprazole 10-30 mg/day, and for the control group, we used the electric spasm therapeutic instrument, Thymatron®IV Systems up to 6 times, 3 times a week. The levels of interleukin (IL)-10, IL-4, IL-6 and IL-1 were detected before and after treatment by ELISA. The positive and negative symptom scale (PANSS) was used to evaluate the efficiency. Before the treatment, IL-1 and IL-6 levels of drug and combined groups were significantly higher than those of the control group ($P<0.05$), while IL-4 and IL-10 had no difference with the control group. There was no significant difference of each factor between the drug and combined groups. After treatment, IL-1, IL-6 and IL-10 of the drug group did not change compared to the levels before treatment, but IL-4 increased significantly; IL-1 and IL-10 of the combined group did not change, while IL-4 and IL-6 increased significantly; IL-1, IL-4 and IL-6 of the drug and combined groups were significantly ($P<0.05$) higher than those in the control group, but not IL-10. IL-1, IL-4 and IL-6 levels of the combined group were significantly higher ($P<0.05$) than those of the drug group. After treatment, the PANSS

scores of the two groups decreased and the combined group decreased more significantly ($P<0.05$). The reduction rate of the combined group was significantly higher ($P<0.05$) than that of the drug group. The total efficiency of the combined group was significantly higher than that of the drug group, and after comparing these levels, there was statistical significance ($P<0.05$). IL-1, IL-4, IL-6 and IL-10 levels of the drug and combined groups before treatment were not associated with PANSS scores and the variation of IL-1, IL-4, IL-6 and IL-10 of the drug and combined groups had no correlation with the reduction rate of the PANSS. The results showed that, cell factors of schizophrenia had an abnormal expression, and medication and MECT can affect the expression level. In addition, MECT can improve the effect in the treatment of schizophrenia, but had no obvious correlation with the change of cell factors.

Introduction

Epidemiological studies have indicated that infection and autoimmune disorders are the dangerous factors of schizophrenia (1). The cell factors of schizophrenic patients especially pro-inflammatory may have abnormal expression (2). Cell factors can affect the human brain and behavior through immune, biochemical and neuroendocrine activities (3). Modified electric convulsive treatment (MECT), also known as non-convulsive (NC)-ECT, is considered an important physical therapy for mental diseases with the advantages of safety, quick-acting and efficiency (4), albeit the mechanism of NC-ECT is not clear. It has been argued that electric convulsive treatment changed the neuroendocrine function of the hypothalamus, and had curing effect through the hypothalamic-pituitary-adrenal axis/thyroid, or it altered the regulatory brain tissue sensitive receptor to have effect (5). Other authors have argued that electric convulsive treatment altered the brain function, especially the cerebral blood flow, to increase the permeability of the blood-brain barrier, thus enhancing the acceptability of drugs to brain receptors (6). In addition, there is evidence that, electric convulsive treatment is similar to antidepressants, which can increase the level of norepinephrine, and the sensitivity of α_1 receptors and serotonin agonist, but decreases the sensitivity of presynaptic α_2 receptor, so as to increase the binding of 5-HT receptor in the cerebral cortex (7). Thus, NC-ECT may induce a change in the diversity of neurobiochemistry.

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Recent studies suggested that NC-ECT, can cause the changes of interleukin (IL)-6, IL-1, IL-5, CRP of depressed patients (8). The present study assumes that NC-ECT may also affect the treatment results by changing cell factors related to schizophrenia, especially IL.

Patients and methods

Patient information. We continuously selected 156 patients who were first diagnosed with schizophrenia at the Bethune International Peace Hospital of PLA (Clinical Branch no. 256, Hebei, China) from January 2013 to January 2016, in line with the diagnostic criteria for schizophrenia in the tenth edition of the International Classification of Diseases. We eliminated those with severe underlying diseases such as hypertension, diabetes, cardiovascular and cerebrovascular disease, liver and kidney dysfunction, autoimmune diseases, pregnant and lactating women who did not tolerate anti-psychotic drugs and NC-ECT treatment, those that voluntarily dropped out of the study or were involved in other studies, as well as any individuals with unhealthy clinical data. The present study was approved by the ethics committee of the Bethune International Peace Hospital of PLA, patients or their families. According to their treatments, they were divided into drug group (70 cases) and drug combined with MECT group (combined group). In addition, 70 cases of healthy volunteers (control group) were selected according to the closest matching method based on 1:1 of age and gender; and 86 cases according to age and gender 1:1 the closest matching method in 70 cases of healthy volunteers (control group). The drug group was composed of 33 male patients and 37 female patients, aged from 45 to 73 years. Their average age was 60.5 ± 14.2 years; the duration of disease was 1-13 months, and the average was 5.6 ± 2.4 months. There were 36 cases mainly with positive symptoms, and 34 cases of negative symptoms. The combined group consisted of 42 male patients and 44 female patients aged from 43 to 75 years. Their average age was 62.2 ± 15.6 years. The course of disease was 2-16 months, and the average was 6.0 ± 2.8 months. There were 40 cases with positive symptoms and 46 cases of negative symptoms. In the control group, there were 32 males and 38 females, aged from 42 to 77 years. Their average age was 63.3 ± 16.3 years. The data collected from different groups were comparable.

Research methods. Drug treatment consisted of anti-psychotic drugs, such as risperidone 2-8, quetiapine 300-750, ziprasidone 80-160 or aripiprazole 10-30 mg/day; for the control group, we used the electric spasm therapeutic instrument, Thymatron® IV Systems (Somatics, LLC, Venice, FL, USA) and DGX mode, firstly placing electrodes on double temporal region of the patients and giving them intravenous anesthesia and neuromuscular blockade according to the weight of patients and the standard of etomidate fat emulsion 0.15 mg/kg of their weight. After anesthesia was completed, limb fasciculation disappeared, muscles were loosened, and the treatment began. The treatment was administered up to 6 times, 3 times a week.

Observation index and detection method. ELISA method was used to detect the levels of IL-1, IL-4, IL-6 and IL-10 before

and after the treatment. We drew 5 ml blood of peripheral elbow following fasting, the blood was centrifuged for 10 min at the speed of 3,000 r/min and preserved at -20°C . We used the kits produced by Shanghai Chen Yi Biological Technology Co., Ltd., and RT-6100 type enzyme standard analyzer of Rayto Life and Analytical Sciences Co., Ltd. (Nanshan, Shenzhen, China) in strict accordance with the advise given in the kits.

The positive and negative symptom scale (PANSS) was used to evaluate the effect, including the total score of PANSS, the reduction rate and the effective rate. The reduction rate was indicated as: $>75\%$ indicated complete remission, $50-75\%$ significant improvement, $25-50\%$ improvement, and $<25\%$ invalid. PANSS had 30 items including positive scale of 7 items (P1-P7), negative scale of 7 items (N1-N7), and general psychopathology table of 16 items (G1-G16). All the items were assessed in the mode of 7 levels from 1 to 7. The α coefficients of each scale varied from 0.83 to 0.73, the split half reliability was 0.80, and the re-test reliability index varied from 0.77 to 0.89.

Statistical analysis. The statistics analysis was made by SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA), measurement data are expressed as mean \pm standard deviation, single factor ANOVA analysis was used in the comparisons between different groups, paired t test was used in inter-comparison; The data were expressed as percentage, the comparison between groups were tested by χ^2 , ranked data were compared by the rank sum test. The Pearson test was used for the related analysis of measurement. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Changes of cell factors before and after treatment. Before treatment, IL-1 and IL-6 levels of the drug group and combined group were significantly higher than those of the control group, and the differences had statistical significance ($P < 0.05$); compared with the control group, where the differences of IL-4 and IL-10 had no statistical significance. The difference of each factor of the drug and combined groups had no statistical significance. The differences of IL-6, IL-10 and IL-1 of the drug group before treatment and after treatment had no statistical significance while IL-4 significantly increased. The differences of IL-1 and IL-10 levels of the combined group were not statistically significant compared to those before treatment while IL-4 and IL-6 were significantly increased. The difference of each factor of the control group before and after treatment had no statistical significance. After treatment, IL-1, IL-4 and IL-6 of the drug and combined groups were significantly higher than those in the control group, and the differences had statistical significance ($P < 0.05$). The difference of IL-10 compared with the control group was not statistically significant. IL-1, IL-4 and IL-6 levels of the combined group were significantly higher than those of the drug group, and the differences had statistical significance ($P < 0.05$) (Table I).

Comparison of treatment effects. After comparing the PANSS scores of the two groups before treatment, the difference was not statistically significant. PANSS scores of the two groups after treatment decreased, the combined group decreased more

Table I. Changes of cell factors before and after treatment (pg/ml).

Group	IL-1		IL-4		IL-6		IL-10	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Drug	52.8±16.9	53.0±17.2	6.3±2.4	8.5±2.6	16.3±4.0	16.6±4.3	15.7±4.5	15.8±5.0
Combined	54.6±15.8	55.8±14.4	6.5±2.3	12.8±3.6	17.5±4.2	24.3±4.5	15.8±4.4	15.7±5.3
Control	33.6±13.2	33.3±12.8	6.6±2.5	6.5±2.6	7.2±2.6	7.0±2.5	15.6±4.3	15.5±5.2
F-value	8.630	9.302	0.632	8.527	7.852	12.635	0.231	0.632
P-value	<0.001	<0.001	0.548	<0.001	<0.001	<0.001	0.965	0.549

IL, interleukin.

Table II. Comparison of PANSS scores.

Group	Before treatment PANSS score	After treatment PANSS score	The reduction rate (%)
Drug	93.2±15.6	78.5±12.3	38.5±7.6
Combined	93.5±15.4	60.4±12.2	56.3±8.3
t-test	0.635	9.637	12.534
P-value	0.427	<0.001	<0.001

PANSS, positive and negative symptom scale.

Table III. Comparison of efficiency.

Group	Cases	Complete remission	Significant improvement	Improvement	Without efficiency	Efficiency
Drug (n,%)	70	5 (7.1)	13 (18.6)	23 (32.9)	29 (41.4)	41 (58.6)
Combined (n,%)	86	17 (19.8)	21 (24.4)	26 (30.2)	22 (25.6)	64 (74.4)
χ^2				8.016		4.404
P-value				0.046		0.036

significantly, and the difference had statistical significance ($P<0.05$). The reduction rate of the combined group was significantly higher than that of the drug group, and the difference was statistically significant ($P<0.05$) (Table II). The total effective rate of the combined group was significantly higher than that of the drug group, and was statistically significant ($P<0.05$) (Table III).

Related analysis. IL-1, IL-4, IL-6 and IL-10 levels of the drug and combined groups had no correlation with the PANSS score before treatment and the variation of IL-1, IL-4, IL-6 and IL-10 of the drug and combined groups had no correlation with the reduction rate of the PANSS.

Discussion

Cytokine is a type of soluble small molecule protein, which plays an important role in the regulation of immune system. Interleukin is a cell factor secreted by T-cells, which can be

divided into pro-inflammatory interleukins such as IL-1, IL-6, and anti-inflammatory ILs such as IL-4 and IL-10 (9-11). It has been confirmed that, pro-inflammatory ILs can affect the dopamine and the pathway and cognitive process of glutamate to cause pathological and physiological changes in patients with schizophrenia (12). In addition, cell factors can affect any pathological and physiological changes in patients with schizophrenia by triggering other physiological responses, such as the activation of the hypothalamic pituitary adrenal axis (13). It has been suggested that, the disorder of inflammatory cell factors and anti-inflammatory cell factors can cause pathological and physiological changes in patients with schizophrenia (14). Serum/plasma cell factors are induced by blood cells and endothelial cells, and may be derived from the brain. The abnormal expression of cell factors is an important marker of inflammatory activity (15).

As a pro-inflammatory cell factor, IL-1 can affect the neural degeneration and neural protection in the brain, participate in the regulation of synaptic plasticity, and in the

central nervous system regulating the transfer of dopaminergic neurotransmitter (16). Previous findings showed that, IL-1 of schizophrenia patients had an abnormal expression and gene polymorphisms of IL-1 was associated with schizophrenia (17,18). For example, Xu and He (19) studied the single nucleotide variants of IL-1, rs16944 and rs1143634 within the promoter region, and found that schizophrenia was correlated with the alleles of rs16944-G. A number of studies have shown that IL-6 was associated with psychiatric disorders (20). Zalcman *et al* found that IL-6 of schizophrenia patients was always at high level, and found that IL-6 can induce hyperthyroidism, such as for aging, and can cause changes in the mental symptoms related to dopamine (21).

The present study found that before the treatment the levels of IL-1 and IL-6 in the drug and combined groups were significantly higher than those in the control group, and there was no difference of IL-4 and IL-10 in the three groups. After treatment IL-1, IL-6 and IL-10 of drug group did not change compared with those before treatment, but IL-4 increased significantly; IL-1 and IL-10 of combined group did not change, but IL-4 and IL-6 increased significantly; IL-1, IL-4 and IL-6 of drug group and combined group were significantly higher than those of the control group, while IL-10 has no difference, and IL-1, IL-4 and IL-6 levels of combined group were significantly higher than those of the drug group. After treatment, the PANSS scores of the two groups both decreased, and the combined group decreased more significantly. The reduction rate of the combined group was significantly higher than that of the drug group. The total effective rate of the combined group was significantly higher than that of the drug group. Moreover, the cell factors of schizophrenic patients had abnormal expression, among which IL-1 and IL-6 were obvious; drug and MECT affected the expression level; and MECT improved the effect of schizophrenia treatment. The correlation analysis revealed that the treatment effect of the drugs and MECT did not correlate with the changes of cell factors. Nevertheless, the specific mechanism involved remains to be further analyzed.

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