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Effect of adjuvant acupuncture therapy on serum cytokines and neurotransmitters in patients with post−stroke depression

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ABSTRACT

Objective: To study the effect of adjuvant acupuncture therapy on serum cytokines and neurotransmitters in patients with post-stroke depression. **Methods:** Patients with poststroke depression who were treated in Traditional Chinese Medicine Hospital of Yuyang District Yulin City between May 2014 and February 2017 were selected as the research subjects and divided into two groups by random number table, control group of patients received neurotrophy, rehabilitation exercise, antidepressant drugs and other symptomatic treatment, and the acupuncture group received auxiliary acupuncture treatment on the basis of symptomatic treatment. The serum levels of nerve cytokines, inflammatory cytokines and neurotransmitters were detected before treatment as well as 2 weeks and 4 weeks after treatment. **Results:** 2 weeks and 4 weeks after treatment, serum BDNF, NGF, IGF-1, FGF-2, NE, DA and 5-HT levels of both groups of patients were higher than those before treatment while HCY, IL-1β, IL-2, sIL-2R, TNF-α levels were lower than those before treatment, and serum BDNF, NGF, IGF-1, FGF-2, NE, DA and 5-HT levels of acupuncture group were higher than those of control group while HCY, IL-1β, IL-2, sIL-2R, TNF-α levels were lower than those of control group. **Conclusion:** Adjuvant acupuncture therapy for post-stroke depression can increase the secretion of nerve cytokines, reduce the secretion of inflammatory cytokines and regulate the function of monoamine neurotransmitters.

1. Introduction

Stroke, also known as acute cerebrovascular disease, includes ischemic stroke and hemorrhagic stroke, the former mainly includes cerebral hemorrhage and subarachnoid hemorrhage, and the latter mainly includes cerebral infarction and transient ischemic attack. Acute cerebrovascular disease occurs abruptly and progresses quickly, which not only causes nerve damage, but also causes a series of mental symptoms. Post-stroke depression is a common complication in stroke recovery period, it can cause depression, mental retardation and other clinical symptoms, and severe cases may cause depression and suicidal behavior. The pathogenesis of post-stroke depression is not completely clear, and the abnormal secretion of inflammatory cytokines and nerve cytokines as well as monoamine neurotransmitter disorder are thought to be closely associated with the occurrence of depression[1,2]. The traditional Chinese medicine theory holds that poststroke depression belongs to the category of "depression syndrome", viscera deficiency and poor qi movement are the important pathogenesis of depression, and acupuncture and moxibustion can regulate Yin and Yang, calm the heart and nerves as well as promote qi to activate blood[3]. The effect of adjuvant acupuncture therapy on serum cytokines and neurotransmitters in patients with post-stroke depression was analyzed in the following studies.

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2. Case information and research methods

2.1 General case information

A total of 72 patients with post-stroke depression who were treated in Traditional Chinese Medicine Hospital of Yuyang District Yulin City between May 2014 and February 2017 were selected as the research subjects, and all patients are with a clear history of stroke, had symptoms of depression after stroke and are with HAMD score 17 points. Patients complicated by mental disorders and cognitive impairment before stroke and those with awareness disorders after stroke were excluded. The 75 patients were randomly divided into two groups by random number table, each with 36 cases. Acupuncture group included 22 men and 14 women, they were 47-64 years old, 25 cases were with ischemic stroke and 11 cases were with hemorrhagic stroke; control group included 23 men and 13 women, they were 45-65 years old, 26 cases were with ischemic stroke and 10 cases were with hemorrhagic stroke. There was no statistically significant difference in general information between the two groups (P>0.05).

2.2 Therapy

The control group of patients received symptomatic treatment such as neurotrophy, rehabilitation exercise and antidepressants, and antidepressant treatment method was as follows: Doxepin Hydrochloride Tablets, starting dose 50 mg, taken orally 1 time/d, and appropriately increasing the dosage after 1 week if the effect was not significant. Acupuncture group of patients, based on routine symptomatic treatment, received adjuvant acupuncture therapy, and the method was as follows: the Baihui, Sisheng, Shenting, Neiguan, Shenmen and Sanyinjiao acupoints were acupunctured, the acupuncture needle was the HWATO brand and with specifications 0.5-1.5 inches, the Baihui was horizontally inserted backward by 1 inch, Sishencong was horizontally inserted towards the Baihui by 0.5-0.8 inches, Shenting was horizontally inserted by 0.5 inch, the Neiguan was perpendicularly inserted by 1 inch, the Shenmen was perpendicularly inserted by 0.3-0.5 inch and blood vessels should be avoided, Sanyinjiao was perpendicularly inserted by 1.0-1.3 inches, needle-retaining time in each acupoint was 30 min, treatment lasted for 5 d and stopped for 2 d week, and treatment lasted for 4 weeks in a row.

2.3 Serum index detection

Before treatment as well as 2 weeks and 4 weeks after treatment, 3-5 mL of cubital venous blood was collected from two groups of patients and centrifuged to separate serum, and enzyme-linked immunosorbent assay kit was used to determine the levels of BDNF, NGF, IGF-1, FGF-2, HCY, IL-1β, IL-2, sIL-2R, TNF-α, NE, DA and 5-HT.

2.4 Statistical methods

SPSS 16.0 software was used for statistical analysis, data processing between groups was by t test and P<0.05 indicated statistical significance in differences in test results (P<0.05).

3. Results

3.1 Serum nerve cytokine levels

Before treatment as well as 2 weeks and 4 weeks after treatment, analysis of serum nerve cytokines BDNF (ng/mL), NGF (pg/mL), IGF-1 (ng/mL) and FGF-2 levels between two groups of patients was as follows: before treatment, serum BDNF, NGF, IGF-1 and FGF-2 levels were not statistically different between the two groups of patients (P>0.05); 2 weeks and 4 weeks after treatment, serum BDNF, NGF, IGF-1 and FGF-2 levels of both groups of patients were higher than those before treatment, serum BDNF, NGF, IGF-1 and FGF-2 levels of acupuncture group were higher than those of control group, and differences in serum nerve cytokine levels were statistically significant within group before and after treatment as well as between groups after treatment (P<0.05).

Table 1.

Changes in serum nerve cytokine levels before and after treatment.

Groups	n	Time	BDNF	NGF	IGF-1	FGF-2
Acupuncture group	36	Before treatment	7.80±0.93	279.3±33.6	29.35±3.62	4.31±0.56
		2 weeks after treatment	13.41±1.85△▲	381.3±45.9△▲	42.56±6.28△▲	6.49±0.78△▲
		4 weeks after treatment	16.58±2.36△▲	452.6±61.5△▲	55.41±7.49△▲	7.51±0.93△▲
Control group	36	Before treatment	7.76±0.89	281.2±36.2	29.14±3.35	4.28±0.52
		2 weeks after treatment	9.67±1.06△	325.6±42.8△	35.26±4.92△	5.06±0.72△
		4 weeks after treatment	11.38±1.44△	379.3±48.9△	39.58±5.41△	5.85±0.68△

△: comparison between before and after treatment, P<0.05; ▲: comparison between acupuncture group and control group, P<0.05.

3.2 Serum inflammatory cytokine levels

Before treatment as well as 2 weeks and 4 weeks after treatment, analysis of serum inflammatory cytokines HCY (nmol/mL), IL-1 β (pg/mL), IL-2 (pg/mL), sIL-2R (pmol/mL) and TNF-α (pg/mL) levels between two groups of patients was as follows: before treatment, serum HCY, IL-1 β, IL-2, sIL-2R and TNF-α levels were not statistically different between the two groups of patients (P>0.05); 2 weeks and 4 weeks after treatment, serum HCY, IL-1 β, IL-2, sIL-2R and TNF-α levels of both groups of patients were lower than those before treatment, serum HCY, IL-1 β, IL-2, sIL-2R and TNF-α levels of acupuncture group were lower than those of control group, and differences in serum inflammatory cytokine levels were statistically significant within group before and after treatment as well as between groups after treatment (P<0.05).

3.3 Serum neurotransmitter levels

Before treatment as well as 2 weeks and 4 weeks after treatment, analysis of serum neurotransmitters NE, DA and 5-HT levels between two groups of patients was as follows: before treatment, serum NE, DA and 5-HT levels were not statistically different between the two groups of patients (P>0.05); 2 weeks and 4 weeks after treatment, serum NE, DA and 5-HT levels of both groups of patients were higher than those before treatment, serum NE, DA and 5-HT levels of acupuncture group were higher than those of control group, and differences in serum neurotransmitter levels were statistically significant within group before and after treatment as well as between groups after treatment (P<0.05).

4. Discussion

Post-stroke depression is a common complication in stroke recovery, multiple physical symptoms and psychiatric symptoms will occur, and severe cases may cause depression and suicidal behavior. The generation of depression in the process of stroke rehabilitation is related to the abnormal secretion of nerve cytokines and inflammatory cytokines as well as the dysfunction of a variety of monoamine neurotransmitters after cerebral ischemic damage or hemorrhagic injury[4]. In clinical practice, conventional antidepressants and neurotrophic drugs can promote neurologic recovery and improve depression to a certain extent, but the effect is not ideal. Acupuncture is a traditional Chinese medicine treatment in recent years. It is used in the treatment of nervous system diseases and psychiatric diseases[5]. Poststroke depression belongs to "depression syndrome" category of TCM, the obsessing caused by viscera deficiency and poor qi activity is the main pathogenesis of the disease, and using acupuncture to stimulate the Baihui, Sisheng, Shenting, Neiguan, Shenmen, Sanyinjiao and other acupoints can effectively regulate qi activity, as well as calm the nerves and restore consciousness[6]. Study has reported that acupuncture treatment has significant improving value for the depression in patients with poststroke depression[7], but the specific molecular mechanism for acupuncture and moxibustion to improve depression in patients with poststroke depression is not elucidated.

As a stimulus signal, acupuncture can cause the nerve endings to produce the action potential and release the nerve impulses, which can be transmitted to the central nervous system and then regulate the secretion of the corresponding nerve cytokines. BDNF and NGF are the cytokines specifically act on neurons, the former is has the effects of promoting the damaged neuron regeneration and differentiation, and can maintain the physiological functions of central nerves and promote the repair of damaged nerve function, and the latter has the remarkable effect on nourishing nerves and promoting nerve growth, and can improve the nutritional status of neurons and induce the axon growth[8]; IGF-1 is an important cytokine that promotes growth in the body, which is mainly synthesized by liver and can pass through the blood-brain barrier, act on the receptor in brain tissue and regulate the neural function[9]; FGF2 is a kind of cytokine that regulates the survival and proliferation of neurons, glial cells and endothelial cells, and it has promoting effect on the establishment of collateral circulation and the regeneration of nerve cells in the process of stroke rehabilitation[10]. In the study, analysis of the changes in serum contents of nerve cytokines before and after treatment showed that serum BDNF, NGF, IGF-1 and FGF-2 levels of both groups of patients after treatment were higher than those before treatment, and serum BDNF, NGF, IGF-1 and FGF-2 levels of acupuncture group after treatment were higher than those of

Table 2.

Changes in serum inflammatory cytokine levels before and after treatment.

Groups	n	Time	HCY	IL-1 β	IL-2	sIL-2R	TNF-α
Acupuncture group	36	Before treatment	36.25±4.27	32.52±4.59	85.61±9.35	132.5±16.7	46.41±5.72
		2 weeks after treatment	23.42±3.48△▲	21.39±3.17△▲	48.62±5.24△▲	74.4±8.9△▲	30.29±4.25△▲
		4 weeks after treatment	17.68±1.94△▲	17.53±2.18△▲	34.25±4.58△▲	50.3±7.2△▲	23.41±3.25△▲
Control group	36	Before treatment	36.78±5.51	33.10±4.53	86.12±9.27	133.1±14.8	46.86±6.02
		2 weeks after treatment	31.35±4.62△	27.31±3.52△	68.74±8.93△	93.4±11.4△	39.48±4.85△
		4 weeks after treatment	27.62±3.53△	23.75±2.97△	61.32±7.68△	82.6±9.3△	33.25±4.85△

△: comparison between before and after treatment, P<0.05; ▲: comparison between acupuncture group and control group, P<0.05.

Table 3.

Changes in serum neurotransmitter levels before and after treatment.

Groups	n	Time	NE	DA	5-HT
Acupuncture group	36	Before treatment	8.95±1.02	8.01±0.94	7.98±0.93
		2 weeks after treatment	14.51±1.84△▲	13.94±1.67△▲	14.12±1.67△▲
		4 weeks after treatment	17.04±2.25△▲	16.78±2.05△▲	16.92±2.03△▲
Control group	36	Before treatment	8.87±0.94	8.14±0.98	8.03±0.89
		2 weeks after treatment	11.36±1.42△	10.37±1.16△	11.16±1.49△
		4 weeks after treatment	13.31±1.69△	12.94±1.42△	13.05±1.48△

△: comparison between before and after treatment, P<0.05; ▲: comparison between acupuncture group and control group, P<0.05.

control group. That means that conventional therapy can improve the secretion of nerve cytokines in patients with post-stroke depression to a certain extent, and the combination of adjuvant acupuncture and moxibustion therapy can further promote nerve cytokine secretion and is conducive to improving the nutrition state of neurons.

Inflammation is a common pathological basis in the course of stroke and depression, and the abnormal secretion of inflammatory cytokines will not only cause atheromatous plaque formation and lead to the occurrence of cerebrovascular diseases, but can also affect the function of the cerebral neural network and cause the change of mood. HCY is the product of methionine metabolism in the body, which activates the macrophages and can trigger inflammatory response; IL-1 β , IL-2 and TNF- α are all produced by activated macrophages, which can mediate the cascade activation of inflammatory responses, induce the infiltration of various inflammatory cells in the lesion and promote the secretion of multiple inflammatory mediators[11]. In the study, analysis of the changes in serum levels of inflammatory cytokines before and after treatment showed that serum HCY, IL-1 β , IL-2, sIL-2R and TNF- α levels of both groups of patients after treatment were lower than those before treatment, and serum HCY, IL-1 β , IL-2, sIL-2R and TNF- α levels of observation group after treatment were lower than those of control group. That means that conventional treatment can reduce the inflammatory response in rehabilitation process of patients with post-stroke depression to a certain extent, and the combination of adjuvant acupuncture and moxibustion therapy can inhibit the secretion of inflammatory factors and further reduce the inflammation reaction, which is beneficial to the recovery of neural function and the improvement of the depression.

"Monoamine neurotransmitter hypothesis" is the depression pathogenesis highly recognized at present, and the disorder of the secretion and functions of NE, DA, 5-HT and other monoamine neurotransmitters can lead to emotional dysregulation, and produce the bad emotions such as anxiety and depression. NE is the neurotransmitter that regulates awakening, stress and emotion, and it can maintain the cerebral excitatory state by regulating the brain's response to new environmental stimuli[12,13]; DA can act on the prefrontal cortex and directly cause anxiety[14]; 5-HT is the neurotransmitter that regulates sleep, cognition and emotion, and it regulates mood through acting on the 5-HT1A receptor and 5-HT2 receptor of the post-synaptic membrane[15,16]. The secretion of monoamine neurotransmitters such as NE, DA and 5-HT significantly reduces during post-stroke anxiety. In the study, analysis of the changes in serum levels of monoamine neurotransmitters before and after treatment showed that serum NE, DA and 5-HT levels of both groups of patients after treatment were higher than those before treatment, and serum NE, DA and 5-HT levels of acupuncture group after treatment were higher than those of control group. This means that conventional treatment can reduce the secretion of monoamine neurotransmitters in rehabilitation process of patients with post-stroke depression to a certain extent, and combination of adjuvant acupuncture and moxibustion therapy can further inhibit the monoamine neurotransmitter secretion and improve the depression.

Adjuvant acupuncture and moxibustion therapy for poststroke depression can effectively improve the depression, and the molecular pathways for acupuncture and moxibustion to improve depression are increasing nerve cytokine secretion, reducing inflammatory cytokine secretion regulating monoamine neurotransmitter function.

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