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Original Article

Influence of acupuncture on patients with post-stroke depression and through p11/tPA/BDNF pathway genes

Peng Sang, Jiahui Zhao, Shun Wang, Hui Yang, Huijuan Shi

Department of Five Families of Acupuncture and Moxibustion, Heilongjiang College of Traditional Chinese Medicine, Harbin 150001, Heilongjiang, China

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Abstract: Objective: The aim of this study is to investigate the clinical efficacy of acupuncture therapy on patients with post-stroke depression (PSD). Also, we determined the impact of acupuncture therapy on the optimal interactive model of p11/tissue plasminogen activator (tPA)/brain-derived neurotrophic factor (BDNF) pathway genes. Methods: A total of 200 PSD patients were enrolled according to the diagnostic criteria for stroke in the National Conference on Cerebrovascular Disease, and they were randomly divided into an acupuncture therapy group (n=100) and a conventional therapy group (n=100). Patients in both groups were treated with medical and rehabilitation therapy, and those in the acupuncture therapy group underwent conventional acupuncture therapy additionally for 2 months. The basic data of patients were collected, the psychological and social factors were evaluated using the scale evaluation method, and p11 (rs11204922), tPA (rs8178895, rs2020918) and BDNF (rs6265, rs2049046, rs16917271, rs727155) gene polymorphisms were detected using the TaqMan-MGB probe method. Then, the results of general data, scale evaluation results and gene polymorphisms between the two groups were compared, and the correlation between gene-gene interaction and PSD was analyzed using generalized multifactor dimensionality reduction (GMDR). Results: Acupuncture decreased BMI, HDRS and mRS scores but elevated MMSE score compared to conventional therapy without acupuncture therapy ($P<0.05$). Genotype and allele frequency of 7 SNP were not significantly changed after the treatment of acupuncture. The optimal interactive models of p11/tPA/BDNF pathway in both groups were significantly correlated with PSD ($P<0.01$). We found the cross-validation consistency and balance accuracy in GMDR analysis of the optimal interactive model in the acupuncture therapy group were lower, but the value of the sign test was higher than those in the conventional therapy group. Conclusion: Acupuncture therapy can improve the depressive symptoms of PSD patients and affect the gene expressions in the p11/tPA/BDNF pathway.

Keywords: Post-stroke depression, P11, tPA, BDNF, gene

Introduction

Post-stroke depression (PSD) is a common complication of mental disturbance after stroke, the incidence rate of which is 33% [1]. PSD is often characterized as depression, emotional loss of control and lack of initiative, along with anxiety and cognitive disorder [2]. PSD frequently gives rise to serious adverse effects in health and emotions of stroke patients, which prolongs the rehabilitation time, reduces quality of life and increases the disability and fatality rates. PSD thus brings great psychological pressure on patients and their families, and causes heavy economic consequences. According to recent studies [3-5], genetic susceptibility is implicated in the pathogenesis of PSD, among which, gene inheritance of p11/tissue plasminogen activator (tPA)/brain-derived neurotrophic factor (BDNF) pathway plays a significant role, and the optimal interactive models consist of p11 (rs11204922), tPA (rs8178895, 2020918) and BDNF (rs6265, rs2049046, rs16917271, rs727155) [6]. Currently, the findings of acupuncture application in the treatment of PSD showed that acupuncture therapy can significantly improve the depressive state of PSD patients [7-9]. In this study, we determined the clinical efficacy of acupuncture therapy on PSD patients and its influence on the optimal interactive model of p11/tPA/BDNF pathway genes, so as to provide a genetic basis for acupuncture therapy in PSD.

Materials and methods

Subjects of study

A total of 200 PSD patients treated in Heilongjiang College of Traditional Chinese Medicine from March 2016 to December 2017 were enrolled according to the diagnostic criteria for stroke in the National Conference on Cerebrovascular Disease, including 82 males and 118 females with an average age of (65.34± 8.31) years old. Inclusion criteria: 1) patients who were informed, agreed and were willing to cooperate in the study, 2) patients who met the diagnostic criteria for stroke in the National Conference on Cerebrovascular Disease, 3) patients aged ≤80 years old, 4) patients who suffered from a stroke within 1 year and presented with stable conditions, and 5) patients who did not have disorders in hearing, vision, language and consciousness, presented a certain reading and dictating ability, and who could cooperate to accomplish the examination. Exclusion criteria: 1) patients with stroke accompanied by disturbance of consciousness, or who could not cooperate with the examination due to serious conditions, or 2) patients with serious medical diseases, or severe dysfunction in the heart, liver and kidney. In this study, patients were randomly divided into an acupuncture therapy group and a conventional therapy group. In the acupuncture therapy group (n=100), there were 46 males and 54 females with an average age of (65.42±8.76) years old. In the conventional therapy group (n=100), there were 36 males and 64 females with an average age of (64.21±8.92) years old. Patients in both groups were treated with medical and rehabilitation therapies, and those in the acupuncture therapy group underwent additional acupuncture therapy. The acupoint was selected, positioned and operated according to *Acupuncture & Moxibustion*, and the treatment was performed once a day, 5 times a week (over 2 months as a treatment course). All the patients signed the informed consent before the experiment, and this study was approved by the Ethics Committee of Heilongjiang College of Traditional Chinese Medicine.

Acupuncture intervention

Acupuncture intervention was performed as previously reported [10]. In brief, the patients in the acupuncture therapy group received electroacupuncture on both sides, and acupoints were between ipsilateral Hegu (LI4) and Quchi (LI11) and between ipsilateral Zusanli (ST36) and Taichong (LR3) (Hwarto, SMY-10A, Suzhou, Jiangsu, China). The needles were fixed on the skin with adhesive tape and patients could not observe the acupuncture procedure. The use of low frequency rather than high frequency was adopted and the needles did not actually pierce through the skin, though tingly sensations may appear.

Rehabilitative therapy

Rehabilitation was conducted to maintain and refine skills. Patients were encouraged to utilize stroke-impaired limbs to do exercise, including sitting up, standing, walking, bathing, dressing, and using a toilet, with or without assistance.

Research methods

Collection of general clinical data: The name, age, gender, body mass index (BMI), educational level, vascular risk factors (coronary heart disease, hypertension, hyperlipidemia, hyperglycemia, smoking, drinking, etc.), the past history and family history of stroke, and family history and personal history of mental disturbance of the PSD patients were collected.

Evaluation of psychological and social factors: Hamilton depression rating scale (HDRS) was adopted for the severity of depression [11], mini-mental state examination (MMSE) for cognitive function [12], Barthel index (BI) for the recovery of activity of daily living [13], modified Rankin scale (mRS) for the recovery of neurological function [14], and National Institute of Health Stoke Scale (NIHSS) for the functional status [15]. All patients completed the survey under the guidance of a doctor, and all scales were comprehensively evaluated by two strictly-trained and qualified doctors in the Department of Psychiatry and Neurology.

Selection of candidate gene sites: According to the research results of Liang JF et al [6], the optimal interactive models of p11/tPA/BDNF pathway were selected as follows: p11 (rs11-204922), tPA (rs8178895, rs2020918) and BDNF (rs6265, rs2049046, rs16917271, rs727155). Specific genes are shown in **Table 1**.

Gene polymorphism detection: After 1 mL venous blood from the elbow was collected

Table 1. Information about TaqMan®-MGB probe

Gene	Site	Chromosomal position	Gene position	[VIC/FAM] sequence
p11	rs11204922	151958144	Intronic	TGCAGCAGGGTAAGGACCTCTAAAT[C/T]TTAAAAAGGCTAATTTTAGGAGGTT
tPA	rs8178895	42032379	UTR3	CTCCCCTCTCTTGGCCCTCTACATA[C/T]TCATACCTCCATGGAGAGTGCCTTT
	rs2020918	42072438	Intergenic	CCCAGGCCATGGCTGTGTCTGGGGC[A/G]GGCTCCTTTGGGAGAGCGGCCAAAG
BDNF	rs6265	27679916	Exonic	TCCTCATCCAACAGCTCTTCTATCA[C/T]GTGTTCGAAAGTGTCAGCCAATGAT
	rs2049046	27723775	Intronic	CAGCAGTACCGTACTTAACTTGGAG[A/T]CCCTGGACCTCCTCGGAGCATAAAA
	rs16917271	27749548	Intergenic	TCACACCAATTCTTAGGCATGGTTT[A/T]ATCATTTGTGCAATTAAGATACACT
	rs727155	27750449	Intergenic	AGCAGATGCATCCTTGAAGAGGCCT[C/T]GACAGAACCTAGGCCAATTCGCTTC

Table 2. Comparison of general data ($\bar{x}\pm s$)/(%)

	Acupuncture therapy group (n=100)	Conventional therapy group (n=100)	t/χ^2	*P*
Age (years old)	65.42±8.76	64.21±8.92	0.823	0.392
Gender (male/female)	46/54	36/64	2.067	0.151
BMI (Kg/m^2)	23.45±3.24	24.21±2.78	2.547	0.011
Educational level (years)	7.90±4.65	6.64±4.50	0.216	0.601
Coronary heart disease (n)	13 (13.00)	10 (10.00)	0.442	0.506
Hypertension (n)	23 (23)	20 (20.00)	0.267	0.606
Hyperlipidemia (n)	8 (8.00)	9 (9.00)	0.064	0.800
Hyperglycemia (n)	22 (22.00)	20 (20.00)	0.121	0.728
Smoking (n)	37 (37.00)	42 (42.00)	0.523	0.470
Drinking (n)	30 (30.00)	28 (28.00)	0.097	0.755

from patients, deoxyribonucleic acid (DNA) was extracted using the median whole blood genomic DNA extraction kit (Beijing BioTeke Biotechnology Co., Ltd., batch No.: 0020170714) according to instructions of the kit. The genotype of each sample was detected and analyzed using the TaqMan®SNP Genotyping Assays kit (Thermo, batch No.: 1712101). The 10 mL SNP reaction system consisted of 5 mL TaqMan PCR Master Mix (2×), 0.5 mL TaqMan SNP genotyping assay mix, 2.5 mL distilled water, and 2 mL DNA template. The conditions represented denaturation at 95°C and annealing at 60°C for 20 s for 40 cycles on a Roche 480 qPCR cycler (Indianapolis, IN, USA). Specific information about gene site probe are shown in **Table 1**.

Statistical methods

SPSS 20.0 software was used for the statistical analysis. Measurement data were expressed as ($\bar{x}\pm s$). The independent-sample *t* test was adopted for the comparison of measurement data meeting normal distribution between two groups, and chi-square test was used for the comparison of measurement data and enumeration data meeting abnormal distribution. Whether the genotype distribution meets the Hardy-Weinberg equilibrium was analyzed via likelihood-ratio χ^2 test. The genotype and allele frequency were compared in each group using the R×C chi-square test. Generalized multifactor dimensionality reduction (GMDR) was used to analyze the correlation between gene-gene interactions and PSD. $P<0.05$ suggested that the difference was statistically significant.

Results

Acupuncture decreased BMI compared to conventional therapy

In the acupuncture therapy group, BMI was significantly lower than that in the conventional therapy group ($P<0.05$). However, there were no differences in other general data ($P>0.05$) (**Table 2**).

Acupuncture decreased HDRS and mRS scores but elevated MMSE score compared to conventional therapy

After treatment, in the acupuncture therapy group, the HDRS score and mRS score were

Table 3. Comparisons of scales between the two groups after treatment ($\bar{x}\pm s$)

	Acupuncture therapy group (n=100)	Conventional therapy group (n=100)	*t*	*P*
HDRS score	21.75±5.78	23.12±5.63	2.634	0.008
MMSE score	23.68±4.98	19.78±3.97	3.576	0.048
NIHSS score	4.69±4.13	4.78±4.07	1.354	0.178
mRS	2.02±1.43	2.36±1.21	2.059	0.047
BI	2.21±1.49	2.19±1.38	0.043	0.917

Table 4. Comparison of genotype distribution frequency between the two groups [n (%)]

Gene	SNP	Acupuncture therapy group			Conventional therapy group			χ^2	*P*
p11	rs11204922	TT	CT	CC	TT	CT	CC		
		12 (12.00)	50 (50.00)	38 (38.00)	10 (10.00)	47 (47.00)	43 (43.00)	0.583	0.747
tPA	rs8178895	CC	CT	TT	CC	CT	TT		
		3 (3.00)	22 (22.00)	75 (75.00)	1 (1.00)	33 (33.00)	66 (66.00)	3.774	0.151
	rs2020918	AA	AG	GG	AA	AG	GG		
		6 (6.00)	37 (37.00)	57 (57.00)	5 (5.00)	37 (37.00)	58 (58.00)	0.100	0.951
BDNF	rs6265	GG	GA	AA	GG	GA	AA		
		31 (31.00)	51 (51.00)	18 (18.00)	29 (29.00)	56 (56.00)	15 (15.00)	0.573	0.751
	rs2049046	AA	AT	TT	AA	AT	TT		
		18 (18.00)	56 (56.000)	26 (26.00)	19 (19.00)	54 (54.00)	27 (27.00)	0.082	0.960
	rs16917271	AA	AT	TT	AA	AT	TT		
		2 (2.00)	34 (34.00)	64 (64.00)	1 (1.00)	24 (24.00)	75 (75.00)	2.928	0.231
	rs727155	CC	CT	TT	CC	CT	TT		
		19 (19.00)	56 (56.00)	25 (25.00)	17 (17.00)	49 (49.00)	34 (34.00)	1.951	0.377

statistically lower than those in the conventional therapy group ($P<0.05$), but the MMSE score was significantly higher than that in the conventional therapy group ($P<0.05$). No significant differences of NIHSS score and BI were found between the two groups ($P>0.05$) (**Table 3**).

Genotype and allele frequency of 7 SNPs were not significantly changed after the treatment with acupuncture

No differences in genotype and allele frequency of 7 SNPs sites of 3 genes were observed between the two groups ($P>0.05$) (**Tables 4** and **5**).

Acupuncture affects optimal interactive model of p11/tPA/BDNF pathway and PSD

The optimal interactive models of the p11/tPA/BDNF pathway in both groups were significantly correlated with PSD ($P<0.01$), and the cross-validation consistency and balance accuracy in GMDR analysis of the optimal interactive model in the acupuncture therapy group were lower than those in the conventional therapy group, with higher value in the sign test (**Table 6**).

Discussion

PSD has no matching of disease in ancient Chinese medicine, which is roughly classified into the “disease-induced depression” according to its clinical manifestations. Traditional Chinese medicine believes that PSD patients are mostly middle-aged or elderly patients who have deficiency of liver and kidney, deficiency of qi and blood, malnutrition in the brain, stagnant qi-blood circulation after stroke and stagnant cerebral collateral flow due to blood stasis and wind phlegm. Moreover, patients are sorrowful about the disease, and the liver and spleen are damaged due to stagnation of liver qi and over-anxiety, which leads to malnutrition in the brain and marrow, and distraction, as well as PSD. Acupuncture therapy can dredge the channels, promote qi and activate blood, strengthen body resistance and eliminate evil, and disperse stagnated liver qi to relieve depression, which has significant efficacy in improving the neurological impairment and reducing the disability rate of PSD patients. Zhang Lin et al [15] studied and showed that acupuncture combined with auricular point therapy can effectively

Table 5. Comparison of allele distribution frequency between the two groups [n (%)]

Gene	SNP	Acupuncture therapy group		Conventional therapy group		χ^2	*P*
p11	rs11204922	T	C	T	C		
		74 (37.00)	126 (63.00)	67 (33.50)	133 (66.50)	0.537	0.464
tPA	rs8178895	C	T	C	T		
		28 (14.00)	172 (86.00)	35 (17.5)	165 (82.50)	0.923	0.337
	rs2020918	A	G	A	G		
		49 (24.50)	151 (75.50)	47 (23.50)	153 (76.50)	0.055	0.815
BDNF	rs6265	G	A	G	A		
		113 (56.50)	87 (43.50)	114 (57.00)	86 (43.00)	0.010	0.920
	rs2049046	A	T	A	T		
		92 (46.00)	108 (54.00)	92 (46.00)	108 (54.00)	0.000	1.000
	rs16917271	A	T	A	T		
		38 (19.00)	162 (81.00)	92 (46.00)	108 (54.00)	2.679	0.102
	rs727155	C	T	C	T		
		94 (47.00)	106 (53.00)	83 (41.50)	117 (58.50)	1.226	0.268

Table 6. Correlation analysis between optimal interactive model of p11/tPA/BDNF pathway and PSD in both groups (GMDR model)

Group	Interactive model	Cross-validation consistency	Balance accuracy	Sign test (*P*)
Acupuncture therapy group	A1B1B2C1C2C3C4	7/10	0.6798	0.002
Conventional therapy group	A1B1B2C1C2C3C4	8/10	0.7278	0.001

Note: A: p11 gene, B: tPA gene, C: BDNF gene, A1: rs11204922, B1: rs8178895, B2: rs2020918, C1: rs6252, C2: rs2049046, C3: 16917171, C4: rs727155. GDMR analysis is performed, the results are corrected using BMI as a concomitant variable, and the *p* value is replaced and corrected for 1000 times.

attenuate the clinical symptoms of PSD patients. Evidence indicated that acupuncture therapy dredged the governor meridian combined with psychological adjustment and reduced the damage duration of PSD. It therefore improves the overall efficacy on PSD, and enhances the clinical compliance [16]. The research on electro-acupuncture therapy demonstrated that it improved PSD, and the efficacy was more significant in the good motion function group [17]. Results from our study revealed that after acupuncture therapy, the acupuncture therapy group, had BMI, HDRS scores and mRS score that were lower than those in the conventional therapy group, but the MMSE score was higher than that in the conventional therapy group; indicating that the weight of PSD patients declined, the depression degree was reduced, the neurological function recovered and cognition improved after acupuncture therapy. However, the activity of daily living and functional status of patients have no obvious improvement, because for the NIHSS and BI scores there were no significant differences between the two groups in this study, which is consistent with research results of other scholars. Therefore, it is believed that acupuncture therapy can improve the prognosis of PSD patients.

As a regulator initiating tPA activity, p11 can mediate the metabolism of BDNF and affect the pathological process of PSD through modulation of the tPA activity, thus it exerts an antidepressant effect. Several studies have demonstrated that p11, tPA and BNDF genes play roles in the occurrence of PSD [18, 19]. With the rapid development of gene detection techniques in recent years, significant progress has been made in the analysis of gene sites. It was found in a study on mental disturbance that inheritance is not confined to a single site of a single gene, but ubiquitously inclined to multiple sites of multiple genes. In some complex diseases, gene networks and pathways are likely to affect the occurrence of diseases through gene-gene interactions [20]. Based on the previous finding [6], 7 SNPs sites of 3 genes

of the optimal interactive model of genetic inheritance were selected in this study to explore the influence on p11/tPA/BDNF pathway genes after acupuncture therapy, and the genotype and allele frequency of the 7 SNPs sites of the 3 genes showed no differences between the two groups, suggesting that the 7 SNPs sites of the 3 genes alone have no correlations with the formation of PSD, and further proving that mental disturbance is not just the inheritance of a single gene or a single site. Accordingly, the gene-gene interaction was further analyzed using GDMR. The results showed that the optimal interactive models of p11/tPA/BDNF pathway in both groups were significantly correlated with PSD ($P<0.01$), which provides experimental evidence proving that PSD is caused by gene-gene interactions, and offers evidence confirming that the p11/tPA/BDNF pathway genes are involved in the occurrence of PSD, and that mental disturbance is induced by the combined effect of multiple genes [21]. In addition, it was also found that the cross-validation consistency and balance accuracy of an optimal interactive model in the acupuncture therapy group were lower than those in the conventional therapy group, with higher value of a sign test, indicating that acupuncture therapy affects the expressions of the p11/tPA/BDNF pathway genes, thus changing the interactive model of PSD.

Conclusion

Our data demonstrate that acupuncture therapy can improve the depressive symptoms of PSD patients and affect the gene expressions of p11/tPA/BDNF pathway, which provides fundamental leads for the future treatment of PSD.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Peng Sang, Department of Five Families of Acupuncture and Moxibustion, Heilongjiang College of Traditional Chinese Medicine, No. 23 Xidazhi Street, Nangang District, Harbin 150001, Heilongjiang, China. Tel: +86-0451-87588511; Fax: +86-0451-87588511; E-mail: Pengsang4tr@163.com

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