Characteristics of traditional Chinese medicine syndromes in post-stroke depression

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Objective: To explore the main characteristics of syndromes in traditional Chinese medicine (TCM) in post-stroke depression (PSD) and to provide basis for treatments with TCM herbs.

Methods: According to diagnostic criteria of PSD, stroke patients and depression patients from Department of Neurology, First Affiliated Hospital, Anhui University of Traditional Chinese Medicine were assigned into cerebral stroke group (150 cases), depression group (151 cases) and PSD group (123 cases). Neuropsychological assessments and imaging and biochemical analyses were conducted. TCM syndrome differentiation for these diseases was performed. We also determined the characteristics of TCM syndromes of PSD, relative risk of the syndromes and their correlations with ages as well.

Results: Scores of qi stagnation and blood stasis, liver qi depression, and transformation of fire due to qi stagnation in PSD group were significant higher than those in cerebral stroke group (P<0.05, P<0.01). In cerebral stroke group, majority of the patients displayed one syndrome, while in PSD and depression groups, the patients had three or more syndromes. Of these syndromes, the incidence rate of syndrome of liver qi depression complicated with transformation of fire due to qi stagnation or flaring of fire due to yin deficiency was high. The syndrome of liver qi depression occurred much more frequently in PSD group and depression group than in cerebral stroke group (P<0.05, P<0.01). The logistic regression analysis showed that the syndrome of qi stagnation and blood stasis had high relative risk to PSD. The syndrome of deficiency of heart and spleen was positively correlated with age in cerebral stroke group.

Conclusion: The main TCM syndromes of PSD and depression are qi stagnation and blood stasis, liver qi depression, and transformation of fire due to qi stagnation. The syndrome of deficiency of heart and spleen is closely related to age among the stroke patients. The syndrome of qi stagnation and blood stasis serves as an independent risk factor for PSD. The more complicated the syndromes are, the more serious depression becomes.

Keywords: cerebral stroke; depression; qi stagnation; blood stasis; liver qi depression

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Original Clinical Research

脑卒中后抑郁症的中医证候特征

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目的：探讨脑卒中后抑郁症的中医证候特征，为中药治疗脑卒中后抑郁症提供辨证依据。

方法：对在安徽中医药大学第一附属医院神经内科就诊的病人进行神经功能、影像学、生化及神经心理检查。

根据脑卒中后抑郁症诊断标准，分为脑卒中后抑郁症、抑郁症组和脑卒中组，并对患者进行中医辨证。分析评价脑卒中后抑郁症的中医证候特征及其对脑卒中后抑郁症的危险度，以及中医证候与年龄的相关性。

结果：脑卒中后抑郁症组气滞血瘀证、肝气郁结证及气郁化火证积分显著高于脑卒中组（P＜0.05，P＜0.01）。

脑卒中组主要以单证居多，而脑卒中后抑郁症和抑郁症组患者中，以3证及以上的复合证居多，其中肝气郁结证合气滞血瘀证及阴虚火旺证的比例较高，脑卒中后抑郁症和抑郁症组患者肝气郁结证的频率显著高于脑卒中组（P＜0.05，P＜0.01）。

结论：脑卒中后抑郁症的主要证候特征是气滞血瘀、肝气郁结及气郁化火，其中脑卒中患者心脾两虚证具有年龄依赖性，而气滞血瘀证可以作为脑卒中后抑郁症独立的危险因素，证候越复杂，患者的抑郁程度越重。

关键词：脑卒中；抑郁症；气滞；血瘀；肝气郁结

Stroke is a common neurological disease. It was estimated that there were 5 to 6 million stroke patients in China[^11]. It frequently causes disability and mortality and has high recurrence rate[^11]. In addition, previous studies indicated that 40% to 60% stroke patients developed depression, showing depressed emotion, slow thinking, and reduction in words and movements[^24]. This syndrome is called post-stroke depression (PSD). It showed that the development of PSD was closely related to physical, psychological, intellectual, and (or) social disabilities due to stroke[^24]. In addition, the impairment of the emotion feedback loop in the brain may also contribute to the development of depression[^10].

PSD not only causes emotional pain but also affects physical and cognitive recovery. Thus, it remarkably decreases life quality of the patients. Incidence rate of PSD is high in China. However, because we mostly focus on the physical disabilities caused by stroke, psychological disorders associated with the disease are often overlooked. Therefore, PSD patients are frequently misdiagnosed. In traditional Chinese medicine (TCM), criteria for syndrome differentiation diagnosis of PSD are lacking, affecting the diagnosis and prognosis of this disease when treating PSD patients with TCM therapy. Here, we studied the main TCM syndromes in PSD patients in order to provide basis for TCM treatment of this disease.

1 Clinical data and methods

1.1 Clinical data

1.1.1 Study object All patients with age from 35 to 82 years in this study were from Department of Neurology in the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine.

1.1.2 Diagnostic criteria Stroke patients were diagnosed according to the diagnosis standards (revised edition) approved in the Fourth National Conference in Cerebrovascular Diseases of Chinese Medical Association[^11]. TCM syndrome type was identified according to reference[^15]. The depression behavior was diagnosed by using Beck Depression Inventory (BDI) of multi-mode approach design (MMAD) and Hamilton Rating Scale for Depression (HRSD).

1.1.3 Including criteria Stroke patients were diagnosed according to the above diagnostic criteria. The diagnoses were confirmed by CT or MRI. The HRSD of the patients included should be more than 8.

1.1.4 Excluding criteria Patients with following conditions were excluded from the study: 1) individual or family history of psychological diseases; 2) brain damage or surgery; 3) within 2 months, acceptance of medication for immune system modulation, antidepressive or emotional stability; 4) abusing drugs or alcoholic drinks; 4) history of endocrine diseases, epilepsy, cognitive or intellectual dysfunction; 5) within 3 months, acceptance of medication of licorice, corticoid drugs, or adrenocorticotropic hormone (ACTH) drugs.

1.2 Study methods

1.2.1 Study design Based on the diagnostic criteria, the patients were assigned into different research groups: cerebral stroke group (150 cases), depression group (151 cases) and PSD group (123 cases).

1.2.2 Observed indexes Patients were examined for imaging, biochemistry, neurological function, and neuropsychological function. We then evaluated seven TCM syndromes in these groups using TCM diagnostic scale and diagnostic criteria. The seven TCM syndromes in this study were as follows: liver qi depression, transformation of fire due to qi stagnation, anxiety impairing spirit, deficiency of heart and spleen, flaring of fire due to yin deficiency, stagnation of phlegm and qi, qi stagnation and blood stasis[^15]. We added the maximal score of each item in the
TCM diagnostic scale to get the total score for each syndrome. The maximal score for each syndrome was 30. Patients with score of 7 or more were considered positive, which was respectively set as mild (7 to 14 scores), moderate (15 to 22 scores), and marked (23 to 30 scores).

1.3 Statistical analysis SPSS 13.0 statistic analysis software was used for all analyses. T-test was used for two group comparison, and one-way ANOVA was used for multi-group comparison. If the variable could not meet normal distribution and homogeneity of variance, failure data analysis should be used. Chi-square test was used for comparison of enumeration data. Bivariate correlation analysis test was used for correlation analysis. Logistic regression was used for relative risk analysis.

2 Results

2.1 Baseline data We studied 123 PSD patients (65 males and 58 females) with average age of (65.4±7.34) years, 151 depression patients (73 males and 78 females) with average age of (66.8±8.22) years, and we also observed another 150 cerebral stroke patients (85 males and 65 females) with average age of (62.96±8.99) years. There were no significant differences in age and gender among these three groups (P > 0.05). We conducted cognitive tests to ensure the patients had proper visual and auditory abilities in the studies.

2.2 TCM syndrome score The score of qi stagnation and blood stasis in PSD group was significantly higher than that in cerebral stroke group (P=0.033), but significantly lower than that in depression group (P=0.022). The score of liver qi depression in PSD group was significantly higher than that in cerebral stroke group (P=0.004), while there was no significant difference between PSD group and depression group (P=0.252). The scores of transformation of fire due to qi stagnation in PSD group and depression group were significantly higher than that in cerebral stroke group (P=0.038). There were no significant differences in the scores of other TCM syndromes among the three groups. The information was shown in Table 1.

2.2 Frequency of TCM syndromes The incidence rates of qi stagnation and blood stasis, liver qi depression, and transformation of fire due to qi stagnation in PSD group and depression group were significantly higher than those in cerebral stroke group (P<0.01, P<0.05). The incidence rates of deficiency of heart and spleen, flaring of fire due to yin deficiency, and stagnation of phlegm and qi in the three groups displayed no significant differences (P>0.05). The incidence rate of anxiety impairing spirit in depression group was significantly higher than that in cerebral stroke group (P<0.01). The information was shown in Table 2.

### Table 1 TCM syndrome scores in each group

<table>
<thead>
<tr>
<th>TCM syndrome</th>
<th>Cerebral stroke group (n=150)</th>
<th>Depression group (n=151)</th>
<th>PSD group (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qi stagnation and blood stasis</td>
<td>10.33±3.12</td>
<td>12.85±2.99**</td>
<td>11.55±2.54△</td>
</tr>
<tr>
<td>Transformation of fire due to qi stagnation</td>
<td>8.73±1.69</td>
<td>10.65±1.75*</td>
<td>9.58±2.54*</td>
</tr>
<tr>
<td>Anxiety impairing spirit</td>
<td>8.72±1.50</td>
<td>8.81±2.00</td>
<td>8.95±1.45</td>
</tr>
<tr>
<td>Deficiency of heart and spleen</td>
<td>8.88±2.54</td>
<td>9.13±2.33</td>
<td>9.02±2.48</td>
</tr>
<tr>
<td>Flaring of fire due to yin deficiency</td>
<td>9.45±3.34</td>
<td>9.77±3.13</td>
<td>9.78±3.55</td>
</tr>
<tr>
<td>Liver qi depression</td>
<td>9.22±3.27</td>
<td>11.92±3.22**</td>
<td>11.63±2.79**</td>
</tr>
<tr>
<td>Stagnation of phlegm and qi</td>
<td>9.55±3.66</td>
<td>9.74±2.99</td>
<td>9.56±3.70</td>
</tr>
</tbody>
</table>

* P<0.05, ** P<0.01, vs cerebral stroke group; △ P<0.05, vs depression group.

### Table 2 Frequency of TCM syndromes in each group

<table>
<thead>
<tr>
<th>TCM syndrome</th>
<th>Cerebral stroke group (n=150)</th>
<th>Depression group (n=151)</th>
<th>PSD group (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qi stagnation and blood stasis</td>
<td>43 (28.7)</td>
<td>63 (41.7)**</td>
<td>51 (41.5)**</td>
</tr>
<tr>
<td>Transformation of fire due to qi stagnation</td>
<td>50 (33.3)</td>
<td>76 (50.2)**</td>
<td>56 (45.5)*</td>
</tr>
<tr>
<td>Anxiety impairing spirit</td>
<td>13 (8.7)</td>
<td>30 (19.7)**</td>
<td>12 (9.8)</td>
</tr>
<tr>
<td>Deficiency of heart and spleen</td>
<td>42 (28.0)</td>
<td>41 (27.2)</td>
<td>33 (26.8)</td>
</tr>
<tr>
<td>Flaring of fire due to yin deficiency</td>
<td>41 (27.3)</td>
<td>39 (25.8)</td>
<td>33 (26.8)</td>
</tr>
<tr>
<td>Liver-qi depression</td>
<td>76 (50.7)</td>
<td>94 (62.3)*</td>
<td>75 (61.0)</td>
</tr>
<tr>
<td>Stagnation of phlegm and qi</td>
<td>10 (6.7)</td>
<td>10 (6.6)</td>
<td>8 (6.5)</td>
</tr>
</tbody>
</table>

* P<0.05, ** P<0.01, vs cerebral stroke group.

2.3 Frequency of complicated TCM syndromes

The majority of patients in cerebral stroke group displayed only one TCM syndrome, whereas the majority of patients in PSD or depression groups had more than one TCM syndromes. The number of depression patients with one TCM syndrome in
depression group was significantly fewer than that in cerebral stroke group \((P < 0.05)\). The number of patients with three or more TCM syndromes in PSD or depression group was significantly larger than that in cerebral stroke group \((P < 0.05)\). The information was shown in Table 3.

The incidence rates of qi stagnation and blood stasis complicated with liver qi depression, liver qi depression complicated with transformation of fire due to qi stagnation, or qi stagnation and blood stasis complicated with stagnation of phlegm and qi in PSD group and depression group were higher than those in cerebral stroke group \((P < 0.05)\). The incidence rate of liver qi depression complicated with anxiety impairing spirit in depression group was higher than that in cerebral stroke and PSD groups \((P < 0.05)\).

### 2.4 Relative risk of TCM syndromes to PSD

Logistic regression analysis was employed to assess the relative risk of TCM syndromes to PSD. The result revealed that qi stagnation and blood stasis had high value of relative risk \((\alpha = 0.05, P = 0.015)\), and regression coefficient \(\beta\) was 2.089. Other TCM syndromes of PSD showed no significant correlation with the disease \((P > 0.05)\).

### 2.5 Correlation between TCM syndromes and age

The scores of deficiency of heart and spleen had positive correlation with the age of patients in cerebral stroke group and the correlation constant was 0.224 \((P = 0.012)\). The score of deficiency of heart and spleen in cerebral stroke patients at age of 60 years or older was significantly higher than that in cerebral stroke patients at age less than 60 years \((P < 0.01)\). The information was shown in Table 4.

#### Table 3 Frequency of complicated TCM syndromes

<table>
<thead>
<tr>
<th>TCM complicated syndrome</th>
<th>Cerebral stroke group ((n=150))</th>
<th>Depression group ((n=151))</th>
<th>PSD group ((n=123))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single syndrome</td>
<td>61(40.6)</td>
<td>32 (21.2)*</td>
<td>31 (25.2)</td>
</tr>
<tr>
<td>Two syndromes</td>
<td>54(36.0)</td>
<td>60 (39.7)</td>
<td>40 (32.5)</td>
</tr>
<tr>
<td>Three or more syndromes</td>
<td>35(23.3)</td>
<td>59 (39.1)*</td>
<td>52 (42.3)*</td>
</tr>
</tbody>
</table>

\* \(P<0.05, vs\) cerebral stroke group.

#### Table 4 Scores of TCM syndromes at different ages in each group

<table>
<thead>
<tr>
<th>TCM syndrome</th>
<th>Cerebral stroke group ((n=150))</th>
<th>Depression group ((n=151))</th>
<th>PSD group ((n=123))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qi stagnation and blood stasis</td>
<td>8.95(\pm)1.35 8.48(\pm)2.45</td>
<td>9.69(\pm)1.88 10.66(\pm)2.76</td>
<td>10.45(\pm)3.02 9.76(\pm)2.46</td>
</tr>
<tr>
<td>Transformation of fire due to qi stagnation</td>
<td>11.55(\pm)2.44 11.27(\pm)2.97</td>
<td>11.48(\pm)2.87 11.77(\pm)3.35</td>
<td>11.35(\pm)2.21 11.29(\pm)2.97</td>
</tr>
<tr>
<td>Anxiety impairing spirit</td>
<td>10.77(\pm)2.00 10.17(\pm)1.98</td>
<td>9.91(\pm)2.20 10.15(\pm)1.95</td>
<td>10.35(\pm)3.12 10.37(\pm)2.52</td>
</tr>
<tr>
<td>Deficiency of heart and spleen</td>
<td>10.16(\pm)2.73 12.24(\pm)3.50*</td>
<td>11.37(\pm)2.80 11.45(\pm)2.94</td>
<td>12.24(\pm)3.50 11.06(\pm)3.05</td>
</tr>
<tr>
<td>Flaring of fire due to yin deficiency</td>
<td>9.59(\pm)3.10 9.54(\pm)3.11</td>
<td>10.14(\pm)2.05 9.78(\pm)2.00</td>
<td>9.35(\pm)3.44 10.05(\pm)3.17</td>
</tr>
<tr>
<td>Liver qi depression</td>
<td>10.54(\pm)2.95 10.07(\pm)2.60</td>
<td>10.13(\pm)2.56 10.58(\pm)2.45</td>
<td>9.62(\pm)1.95 9.80(\pm)2.43</td>
</tr>
<tr>
<td>Stagnation of phlegm and qi</td>
<td>8.89(\pm)1.87 9.02(\pm)2.00</td>
<td>9.48(\pm)2.78 9.08(\pm)2.37</td>
<td>9.82(\pm)2.03 9.25(\pm)2.35</td>
</tr>
</tbody>
</table>

\*\* \(P<0.01, vs\) less than 60 years.

### 3 Discussion

PSD is a depression disorder occurring in cerebral ischemia or hemorrhage patients. It is a common complication of acute cerebral ischemia or hemorrhage. The incidence rate of this disease in China was from 30% to 70%[11]. TCM theory attributes cerebral ischemia or hemorrhage to stroke. We consider that PSD is a complication of depression occurring in the stroke patients. Stroke arises due to functional deficiency of both liver and kidney and disorder of qi and blood. These dysfunctions in turn cause numbness and clog in cerebral blood vessels or cerebral hemorrhage, leading to blood stasis. Qi and blood cannot circulate normally in the patients with paralysis. Liver qi depression and qi stagnation worsen blood stasis. As a consequence, it affects spleen and then causes dysfunction of spleen. In addition, blood stasis also enhances qi stagnation, leading to an adverse feedback loop. Our current study revealed that qi stagnation and blood stasis was the most common TCM syndrome in PSD patients, and liver qi stagnation and transformation of fire due to qi stagnation were the second and third most common TCM syndromes in PSD patients. We also found that liver qi depression and transformation of fire due to qi stagnation were the major TCM syndromes in PSD and depression patients.

Furthermore, our study demonstrated that the TCM syndrome of qi stagnation and blood stasis complicated with stagnation of phlegm and qi could be used in differential diagnosis of cerebral stroke, PSD, and depression. We found that PSD, with many TCM syndromes, had multiple
pathological causes. Several pathogenic factors stimulated one another and contributed to the development of the disease. In cerebral stroke group, most patients showed only one TCM syndrome but in PSD and depression groups, most patients displayed three or more TCM syndromes, suggesting that TCM multi-syndromes were likely to cause depression. Specifically, qi stagnation and blood stasis complicated with liver qi stagnation or stagnation of phlegm and qi and transformation of fire due to qi stagnation complicated with liver qi stagnation were the major complicated TCM syndromes of PSD. Liver qi depression, qi stagnation, phlegm dampness, and blood stasis may affect one another, and eventually impaired cerebral function and lead to depression. Of all these factors, qi stagnation was the critical factor. When qi stagnation occurred together with liver qi depression, and (or) phlegm dampness, and (or) blood stasis, its contribution to the development of depression will be further enhanced. Consistent with this hypothesis, logistic regression analysis of different TCM syndromes of PSD revealed that qi stagnation and blood stasis had a high relative risk to PSD. We supposed that Chinese herbal medicine promoting circulation of qi and blood may contribute to the prevention and treatment of PSD. Further preclinical and clinical studies in such kind of Chinese herbal medicine will provide basis for design of new therapeutic programs for PSD.

In addition, we revealed that deficiency of heart and spleen may have positive correlation with age in cerebral stroke patients. As the age increases, the deficiency of heart and spleen worsens and the symptoms of cerebral stroke patients becomes serious, suggesting that the deficiency of both heart and spleen is age-dependent.

REFERENCES


