AN ANALYSIS OF THE POST-STROKE COGNITIVE IMPAIRMENT COMBINATION LAW OF TRADITIONAL CHINESE MEDICINE SYMPTOM BASED ON THE COMPLEX SYSTEM ENTROPY CLUSTERING METHOD


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Abstract

Objective: To analyze the TCM symptom manifestations of patients with post-stroke cognitive impairment and explore the combination law of its core symptoms. Method: through the collaboration of multi centers, 1451 patients with mild cognitive impairment and mild dementia are incorporated, of which, 838 cases are with mild cognitive impairment and 613 cases mild dementia. After filtering, the occurrence rate of symptoms which is over 10% are retained and inputted to the traditional Chinese medicine inheritance auxiliary platform through standardized “four diagnostic information”. And then there will be an analysis of the rules of symptoms based on complex system entropy clustering method which is software-integrated. Result: after the analysis based on entropy clustering method, it is found that there are 8 symptom collective groups for mild cognitive impairment and 9 symptom collective groups for mild dementia. The syndrome factor combinations that can be extracted are kidney deficiency, qi deficiency and blood stasis, spleen and kidney deficiency, phlegm stasis; kidney deficiency, phlegm stasis, qi deficiency and blood stasis, spleen and kidney deficiency, phlegm stasis and yin deficiency resulting in vigorous fire. Conclusion: syndrome factors of post-stroke cognitive impairment are qi deficiency, blood stasis, phlegm, yang deficiency, yin deficiency and fire. Kidney deficiency, qi deficiency and blood stasis, spleen and kidney deficiency, phlegm stasis and yin deficiency resulting in vigorous fire are typical symptoms of post-stroke cognitive impairment. Number of patients with yin deficiency resulting in vigorous fire, will increase as their disease aggravated.

Keywords: stroke, cognitive impairment, TCM symptom, complex system entropy clustering.

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Introduction

Post-stroke cognitive impairment is a common complication in stroke. It is easily ignored by patients and their families and even ignored by doctors as its early clinical performance is lighter, has longer course of disease and slow progress. Without early detection and control, it has a high risk of transforming into dementia. Traditional Chinese medicine has a unique advantage in improving early symptoms of post-stroke cognitive impairment; it can slow and stop the disease progression. However, its corresponding dialectical criteria and prevention and control system are not available at present. The analysis of its syndromes has been the core and key of the current work.

Symptom is the external performance of pathological changes; it refers to various abnormal feelings which patients themselves can perceive or it can be directly perceived by the doctors’ sense organs such as eyes, ears, nose, and fingers. Syndrome is a group of relative symptoms, and the two is closely connected. Symptom serves as an important basis of TCM diagnosis and differentia-
tion, it is also the foundation and requirement for TCM differentiation and treatment. Syndrome is a key link of TCM differentiation and treatment. The syndrome analysis is a hard yet hot spot of TCM research and it also constitutes an important part of standardized and normalized study of TCM\(^4\). The information obtained from four diagnostic methods by doctors of TCM, namely, observation, auscultation and olfaction, inquiry and pulse-taking is external and objective performance of overall state of the organism. The four diagnostic methods (symptoms) are the main basis of TCM differentiation, but they have such features as vagueness, overlapping, complexity and latency. Syndrome is a complex and macro-system which featured high dimension, high grade and nonlinearity\(^6\). Although some researchers have carried out a series of explosive studies in different aspects, and do have made some progress\(^7\)-\(^14\), syndrome differentiation of post-stroke cognitive impairment has always been lack of objective and normalized standard, which brings many limits to clinical TCM differentiation treatment of post-stroke cognitive impairment and modern TCM studies.

**Clinical materials and methods**

The study is strictly in line with the requirements of clinical epidemiology and based on multi centers and large samples to observe clinically. “Four diagnostic information” of 1451 patients with mild cognitive impairment and mild dementia is collected and with the help of “traditional Chinese medicine inheritance auxiliary platform (V2.5)”, the core symptom combination rules of post-stroke cognitive impairment are tentatively explored based on complex system entropy clustering method, which can be used to analyze data. It can provide a preliminary basis and reference for further study of syndrome factors and their distribution rules, as well as the establishment of dialectical criteria.

**The report is as follows:**

**General materials**

The cases of the study derive from 14 medical institutions and with a time span of January 2011 to September 2013. The 14 medical institutions are Dongfang Hospital of Beijing University of Chinese Medicine, Wangjing Hospital of China Academy of Chinese Medical Sciences, Changchun University of Chinese Medicine affiliated hospital, Shandong University of Chinese Medicine affiliated hospital, TCM Hospital of Hebei Medical University, Peking University People’s Hospital, Chonqing Hospital of Traditional Chinese Medicine, Beijing Shunyi Hospital of Traditional Chinese Medicine, Youanmen health service center in Fengtai, Beijing, Puhuangyu health service center in Fengtai, Beijing, Fangzhuang health service center in Fengtai, Beijing, Rizhao Hospital of Traditional Chinese Medicine in Shandong province, Xinglong Hospital of Traditional Chinese Medicine in Fengtai, Beijing and Xiamen Hospital of Traditional Chinese Medicine. There are altogether 1451 patients being incorporated, of which, 838 cases are with mild cognitive impairment and 613 cases mild dementia.

**Diagnostic criteria**

For the diagnosis of cerebral infarction, we refer to the “Guide of diagnosis and treatment of acute ischemic stroke in China 2010”, which is formulated by cerebrovascular epidemiology group, branch of the Chinese Medical Association Neurology (15). The diagnosis of cognitive impairment refers to the unified standard which is set by NINDS/CSN in 2006(16).

**Incorporating standard**

Conforming to the diagnostic standard; 2 weeks to 6 month since cerebral infarction; clear conscious, enough visual and auditory abilities; coordinating with neuropsychology in the evaluation.

**Excluding criteria**

Cognitive impairment caused by non-cerebral vascular disease (like Alzheimer disease, FTD, Parkinson's disease, brain injury, cerebral hemorrhage, encephalitis, undermining of thyroid function, etc.) The scores of confirmed depression or Hamilton's Depression Scale (HAMD17) are over 17. Those who have clear focal signs and symptoms of nervous system, or other body diseases cannot complete neuropsychological tests; medium and severe dementia.

**Establishment of database**

Information obtained from four diagnostic methods of 1451 patients is inputted to the “platform management” and “clinical collection” module on the traditional Chinese medicine inheritance auxiliary platform to establish database for after-stroke cognitive impairment. After the entry, two
people will work as a group to verify the inputted information, so as to guarantee its accuracy. “Four diagnostic information” of traditional Chinese medicine includes 64 symptoms, 20 tongue manifestations and 10 pulse manifestations. 64 symptoms are formulated by experts based on literature and clinical experience. They include many locations of disease like heart, liver, spleen, lung and kidney; many typical symptoms and clinical information like dizziness and headache resulting from various nature of disease such as qi, blood, yin and yang. 20 tongue manifestations: based on the basic elements of tongue manifestation and make the type of basic elements a goal to collect information in a comprehensive way. The settings of tongue manifestation include four parts: tongue color, tongue shape, tongue coating and sublingual vein. There are 10 pulse manifestations and they include basic elements such as place, numbers, thickness, length, strength, hardness and fluency.

Data analysis
Yang Hongjun, a researcher of the Chinese medicine research institute from China Academy of Chinese Medical Sciences provided “traditional Chinese medicine inheritance auxiliary platform(V2.5)” and its “data analysis” module is used to analyze data, including symptom sequence and clustering.

The occurrence of symptoms of each patient is ordered in descending order and the occurrence rate which is over 10% will be retained. The “symptom clustering” function of medical cases will be chosen and the analysis of clustering will be made (core calculation methods include modified mutual information method(17) and complex system entropy clustering (18,19). Appropriate correlation and degree of punishment should also be chosen and then “extraction combination” button can be clicked and core symptom combination will be found through network visualized display (core calculation method is unsupervised entropy clustering(20).

Result
Frequency statistics of symptoms According to the peripheral symptom, tongue, pulse of the patients, ranking the 838 patients with mild cognitive impairment and 613 patients with mild dementia in syndrome order. 94 kinds of arrangement are received by symptoms from high frequency to low frequency including 57 symptoms whose occurrence rates are more than10% in patients with mild cognitive impairment (Table 1), and 66 symptoms whose occurrence rate are more than 10% in patients with mild dementia (Table 2).

The combination analysis of core symptoms patients with mild cognitive disorder on complex system entropy clustering. The correlation degree is 8; the penalty degree is 2.

<table>
<thead>
<tr>
<th>Table 1: Occurrence rates are more than 10% in patients with mild cognitive impairment.</th>
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<tbody>
<tr>
<td>Table 2: Occurrence rates are more than 10% in patients with mild dementia.</td>
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</table>
According to cluster analysis, there are 52 kinds of combinations of the three core symptoms out of 94 symptoms of patients with mild cognitive disorder and 10 kinds of combinations of four core symptoms, which can be seen in table 3 and table 4.

With the help of “network display” function of software, visualization of a network of core combinations of symptom clustering can be seen in fig 1.

The combination analysis of core symptoms patients with mild dementia-based on complex system entropy clustering. The correlation degree is 8; the penalty degree is 2. According to cluster analysis, there are 37 kinds of combinations of the three core symptoms out of 94 symptoms of patients with mild dementia-based and 12 kinds of combinations of four core symptoms, which can be seen in table 5 and table 6.

Using the function of software’s “network display”, it shows the network visualization of the core combination of symptom clusters in Figure 2.

The first category belongs to kidney deficiency: combination 10 (blurred vision, aversion to cold and cold limbs, pain of limbs, soreness and weakness of waist and knees) + combination 5 (Red tongue texture, white tongue coating, pale red tongue texture, Yellowish tongue coating) + combination 3 (enuresis when cough and laugh, urgent urination, luxated tooth, dribble of urine) + combination 4 (enuresis when cough and laugh, luxated tooth, dribble of urine, much frequent urination)

The second category belongs to Qi deficiency and blood stasis: combination 6 (Red tongue texture, white tongue coating, pale tongue texture) + combination 2 (thin tongue coating, Red tongue texture, white tongue coating).

The third category belongs to the spleen and kidney deficiency, phlegm internal resistance: combination 7 (Physical clumsiness, fatigued limbs and heavy body, Numbness, pain of limbs) + combination 8 (fatigued limbs and heavy body, aversion to cold and cold limbs, pain of limbs, soreness and weakness of waist and knees) + combination 9 (acid reflux and noise, aversion to cold and cold limbs, pain of limbs, soreness and weakness of waist and knees) + combination 1 (Greasy tongue coating, thin tongue coating, dry tongue coating, thick tongue coating).

Table 3: The combinations of three core symptoms patients with mild cognitive disorder on complex system entropy.

<table>
<thead>
<tr>
<th>No.</th>
<th>The combination of core symptoms</th>
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</tr>
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<tbody>
<tr>
<td>1</td>
<td>Vomiting, dry mouth, fatigue</td>
<td>1</td>
<td>Vomiting, dry mouth, fatigue</td>
</tr>
<tr>
<td>2</td>
<td>Dizziness, sweating, pale tongue</td>
<td>2</td>
<td>Dizziness, sweating, pale tongue</td>
</tr>
<tr>
<td>3</td>
<td>Headache, bluish tongue, pale tongue</td>
<td>3</td>
<td>Headache, bluish tongue, pale tongue</td>
</tr>
<tr>
<td>4</td>
<td>Stomachache, vomiting, pale tongue</td>
<td>4</td>
<td>Stomachache, vomiting, pale tongue</td>
</tr>
<tr>
<td>5</td>
<td>Nausea, vomiting, pale tongue</td>
<td>5</td>
<td>Nausea, vomiting, pale tongue</td>
</tr>
<tr>
<td>6</td>
<td>Vomiting, dry mouth, fatigue</td>
<td>6</td>
<td>Vomiting, dry mouth, fatigue</td>
</tr>
<tr>
<td>7</td>
<td>Dizziness, sweating, pale tongue</td>
<td>7</td>
<td>Dizziness, sweating, pale tongue</td>
</tr>
<tr>
<td>8</td>
<td>Headache, bluish tongue, pale tongue</td>
<td>8</td>
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<tr>
<td>9</td>
<td>Stomachache, vomiting, pale tongue</td>
<td>9</td>
<td>Stomachache, vomiting, pale tongue</td>
</tr>
<tr>
<td>10</td>
<td>Nausea, vomiting, pale tongue</td>
<td>10</td>
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</tr>
</tbody>
</table>

Table 4: The combinations of four core symptoms patients with mild cognitive disorder on complex system entropy clustering.

According to cluster analysis, there are 52 kinds of combinations of the three core symptoms out of 94 symptoms of patients with mild cognitive disorder and 10 kinds of combinations of four core symptoms, which can be seen in table 3 and table 4.

With the help of “network display” function of software, visualization of a network of core combinations of symptom clustering can be seen in fig 1.

The combination analysis of core symptoms patients with mild dementia-based on complex system entropy clustering. The correlation degree is 8; the penalty degree is 2. According to cluster analysis, there are 37 kinds of combinations of the three core symptoms out of 94 symptoms of patients with mild dementia-based and 12 kinds of combinations of four core symptoms, which can be seen in table 5 and table 6.

Using the function of software’s “network display”, it shows the network visualization of the core combination of symptom clusters in Figure 2.

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The second category belongs to Qi deficiency and blood stasis: combination 6 (Red tongue texture, white tongue coating, pale red tongue texture) + combination 2 (thin tongue coating).

The third category belongs to the spleen and kidney deficiency, phlegm internal resistance: combination 7 (Physical clumsiness, fatigued limbs and heavy body, Numbness, pain of limbs) + combination 8 (fatigued limbs and heavy body, aversion to cold and cold limbs, pain of limbs, soreness and weakness of waist and knees) + combination 9 (acid reflux and noise, aversion to cold and cold limbs, pain of limbs, soreness and weakness of waist and knees) + combination 1 (Greasy tongue coating, thin tongue coating, dry tongue coating, thick tongue coating).

Fig. 1: Visualization of a network of core combinations of symptom clustering of mild cognitive disorder clustering.
The first category belongs to the kidney deficiency: combination 4 (rapid pulse, red tongue, white coat, no coat or lack of coat) + combination 5 (dry eyes, tinnitus, blurred vision, soreness and weakness of waist and knees) + combination 8 (red-dish tongue, pale tongue, light red tongue, yellowish coat) + combination 11 (fatigue limps, heavy body, short of breath, pain of limbs, soreness and weakness of waist and knees).

The second category is turbid phlegm obstructing internal: combination 7 (chest tightness, preference for sighing, palpitations, chest bloated pain).

The third category belongs to Qi deficiency and blood stasis: combination 2 (wiry pulse, slippery pulse, fine pulse, weak pulse).

The fourth category belongs to spleen and kidney deficiency, phlegm resistance turbid phlegm obstructing internal: combination 9 (fatigue limps, heavy body, lack of strength, lack of strength) + combination 10 (fatigue limps, heavy body, mental fatigue, lack of strength).

The fifth category belongs to yin deficiency with effulgent fire: Combination 1 (aphtha mouth, bitter taste in mouth, sticky and greasy sensation in mouth, fetid mouth odor) + combination 3 (wiry pulse, lack of fluid in tongue, fine pulse, weak pulse) + combination 6 (dry eyes, tinnitus, blurred vision, thirst) + combination 12 (choppy pulse, tongue with petechia or bruise, sublingual vein tortuosity dark tongue).

Table 5: The combinations of three core symptoms patients with mild dementia-based on complex system entropy clustering.

Table 6: The combinations of four core symptoms patients with mild dementia-based on complex system entropy clustering.

Fig. 2: Combination of core symptoms of mild dementia.
Discussions

The relationships of disease, syndrome differentiation and syndromes are inseparable. Diseases are the largest category, which can be expressed as various stages of syndrome and its corresponding symptoms with a dynamic evolution. The syndrome differentiation is the summarization and generalization of the nature of the disease. And syndrome elements constitute the smallest unit of syndromes, which are mainly divided into two major categories as disease location and disease characteristics. Generally speaking, the dynamic combination of the disease location and the disease characteristics forms syndromes, which helps to flexibly guide clinical syndrome differentiation. Therefore, the syndrome and syndrome elements are the key links of the connection of the disease and syndrome, syndrome and symptoms.

Academician Wang Yongyan has proposed that the syndrome is a non-linear complex giant system, with “internal deficiency and external excess, dynamic space-time, multi-dimensional interface” features. One basic way of researches is to determine the diagnosis of syndromes according to the combination of different syndromes elements, with the basic syndrome elements as a point cut, and through the “dimension reduction and degree elevation”. Complex system based on entropy clustering is one of the most commonly used methods of non-linear data mining, and it is widely used in the extraction of syndrome elements of multiple diseases. The superiority of the method is based on the internal correlation between data variables in order to find and summarize characteristics and rules of them.

Although the basic pathogenesis of stroke is quit clear in Traditional Chinese Medicine, the etiology and pathogenesis theory of post-stroke cognitive disorder is still in the exploratory stage. In this study, with a large-sample, multi-center, multi-regional and multi-level collaborative network system, the four diagnostic methods of patient cases were reduced dimension. And after the syndrome elements were extracted, Qi deficiency, blood stasis, sputum, Yang deficiency, Yin deficiency and fire were found the basic pathological elements of the disease. The disease located in the brain, mainly involved kidney, liver and spleen, and is categorized in mixed excessiveness and deficiency, which once again confirmed the exploration of the prede-
cessors on the syndrome elements.

Kidney deficiency, qi deficiency and blood stasis, spleen and kidney deficiency, phlegm obstruction, are the typical syndromes for the post-stroke cognitive disorder patients. Patients with fire excess from yin deficiency will aggravate with the worsen disease condition.

This conclusion can help to clarify the nature of the disease, syndrome differentiation and syndromes development rules. The study of post-stroke cognitive disorder syndrome is still at the initial stage, and need to do more work in further expanding the sample size, using data mining tools, deeply exploring common syndromes distribution and syndromes development rules.

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