CLINICAL STUDY

Correlation between Traditional Chinese Medicine symptom patterns and serum concentration of zinc, iron, copper and magnesium in patients with hepatitis B and associated liver cirrhosis

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Abstract

OBJECTIVE: To investigate the correlation between the patterns of Traditional Chinese Medicine (TCM) syndromes and the serum concentration of zinc, iron, copper and magnesium of patients with chronic hepatitis B (CHB) and hepatitis B virus (HBV)-induced liver cirrhosis.

METHODS: A total of 86 patients were included in the study between March 1, 2009 and January 1, 2010. All were diagnosed with CHB or HBV-induced liver cirrhosis according to the diagnosis standard of the Chinese Medical Association. Fasting serum concentrations of zinc, iron, copper and magnesium were measured. Patients were classified into different patterns of TCM symptoms according to TCM theory and clinical experience.

RESULTS: In the HBV-induced liver cirrhosis group, the mean zinc concentration in patients with the TCM pattern of stagnation of fluid-Dampness was lower than that in patients with obstruction of collaterals by Blood stasis ($P < 0.034$). In the CHB group, the mean magnesium concentration in patients with toxic Heat flourishing was significantly lower than that in those with Damp-Heat in the Liver and Gallbladder, and those with Liver depression and Spleen deficiency ($P < 0.021$). The concentrations of iron and copper showed little difference among the different TCM symptom patterns.

CONCLUSION: The serum zinc and magnesium concentrations correlated with certain TCM patterns of symptoms in patients with HBV-induced liver cirrhosis and CHB. It may be helpful to interpret the pathogenic change in the TCM symptom patterns in liver cirrhosis and CHB, and also to conduct clinical treatment of the diseases based on identified TCM patterns.

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Key words: Hepatitis B; Fibrosis; Serum; Pattern of symptoms; Medicine, Chinese traditional

INTRODUCTION

The hepatitis B virus (HBV) is one of the world’s most prevalent viral infections, with about 2 billion people chronically infected and about 1 million HBV-related deaths annually. Viral suppression is the primary therapy for chronic hepatitis B (CHB) and HBV-induced cirrhosis of the liver caused by HBV infection. Long-term inhibition of HBV can reduce the inflammation of the liver necrosis, slow the progress of liver fibrosis, and reduce the incidence of hepatocellular carcinoma. Therefore, nucleoside analogue treatment is an effective treatment method to control CHB and HBV-induced cirrhosis. HBV invasion often changes the internal environment, so we must pay attention to
These changes and correct any disturbances to help control disease progression. Zinc, iron, copper, and magnesium are elements necessary for maintaining the physiological activities of the human body; they have many physiological functions, such as participating in enzyme structure and metabolism, biochemical reactions, and composing the immune system. A serious imbalance in elements such as zinc, copper, magnesium, and selenium has been reported in CHB patients, and there is also a correlation between some trace elements and liver function. Biochemical function indices such as transaminase, bilirubin, and coagulation time can objectively reflect liver pathology and prognosis when the liver cells are damaged; the clinical symptoms and signs are also associated with the severity of hepatocellular damage.

The Traditional Chinese Medicine (TCM) patterns of symptoms can reflect the nature of the interaction between the disease and the environment in a certain stage; it includes the corresponding symptoms, signs, and tongue and pulse qualities, and can reveal the etiology, disease character, disease location, and disease trend. Previous studies have reported on TCM symptom patterns related to the immune system, liver fibrosis, and HBV-DNA. In the process of hepatocellular damage, the patients’ clinical symptoms and signs, and tongue and pulse qualities can be examined through four diagnostic methods of TCM. These can then be used to classify the patients into different TCM symptom patterns to determine if the TCM patterns reflect the prognostic process of liver disease as well as biochemical indicators. There are few reports on the relationship between TCM symptom patterns and the serum concentrations of zinc, iron, copper, and magnesium. This study aims to investigate the link between the TCM symptom patterns of patients with HBV infection and serum concentrations of zinc, iron, copper, and magnesium.

**MATERIALS AND METHODS**

**Study participants**
This survey was conducted using data from 86 patients who were admitted to the TCM Department of the Affiliated Hospital of Sun Yat-Sen University from March 1, 2009 to January 1, 2010; there were 34 cases of CHB, three cases of chronic severe hepatitis B, and 49 cases of HBV-induced liver cirrhosis. Fasting levels of zinc, iron, copper, and magnesium were measured. We collected and arranged the data immediately, and then classified patients into different TCM symptom patterns. The study was approved by the institutional review board, and each patient gave written informed consent.

**Diagnostic criteria**
Each patient’s Western medicine diagnosis was based on the diagnostic standards amended by three joint committees of the Chinese Medical Association: the Infectious Diseases Committee, the Parasitic Disease Committee, and the Hepatology Committee. The TCM symptom patterns of patients with CHB and HBV-induced liver cirrhosis were diagnosed according to the diagnostic standards amended by the Hepatology Committee of Chinese Medical Ideology, the Digestive Disease Committee of Integrated Traditional Chinese and Western Medicine, and our clinical experience.

**TCM symptom patterns of patients with CHB and chronic severe hepatitis B**

(a) Damp-Heat in the Liver and Gallbladder included the following clinical symptoms and signs: hypochondriac pain and calor, poor appetite, abdominal distension, nausea and vomiting or detesting greasy food, bitter taste, icterus that is bright yellow like orange peel, brown urine, scrotal eczema or testicular swelling and pain, large amounts of foul-smelling yellow leukorrhea, red tongue with yellow greasy fur, wiry and frequent pulse or slippery pulse.

(b) Liver depression and Spleen deficiency included the following clinical symptoms and signs: anxiety and depression, poor appetite and lassitude, distending pain (or scurrying pain) in the lateral thorax or epigastric discomfort, pharyngeal foreign body sensation, belching and acid regurgitation, loose stools, tongue red at the tip and margins with a yellowish coating, wiry pulse.

(c) Disharmony between the Liver and Stomach included the following clinical symptoms and signs: epigastric pain or scurrying pain in lateral thorax, belching and acid regurgitation, nausea and vomiting, depression or dysphoria and irritability, a feeling of compression in the chest, sighing, belching, poor appetite, wiry pulse. These symptoms were aggravated due to worry or exasperation.

(d) Retention of Damp-Heat included the following clinical symptoms and signs: bright yellow icterus, dull fever, thirst without desire to drink, the body feeling heavy, poor appetite, abdominal distension, nausea and vomiting or detesting greasy food, hypochondriac pain and calor, brown urine, viscous or dry stools, red tongue with yellow greasy fur, slippery pulse or rapid pulse.

(e) Toxic Heat flourishing included the following clinical symptoms and signs: bright yellow icterus that developed in a short time, high fever, irritability or coma and delirium, thirst and a preference for cool drinks, abdominal distension or abdominal pain, subcutaneous hemorrhage, nasal bleeding or hematemesis, poor appetite, nausea and vomiting or detesting greasy food, mass ascites, red tongue with yellow greasy fur or a yellow and dry tongue coating, wiry and frequent pulse or full and frequent pulse.
**TCM symptom patterns of patients with HBV-induced liver cirrhosis**

(a) Liver Qi stagnation included the following clinical symptoms and signs: distending pain (or scurrying pain) in the lateral thorax, impetuousness and irritability, thirst and a bitter taste, pharyngeal foreign body sensation, poor appetite, abdominal distension, belching and acid regurgitation, loose stools, spargosis, red tongue with thin and whitish fur or thin and yellowish fur, wiry pulse.

(b) Retention of Damp-Heat included the following clinical symptoms and signs: bright yellow icterus, abdominal distension, edema in the lower extremities, lassitude, oliguria and loose stools, white or yellow greasy fur, slippery pulse or slippery and rapid pulse.

(c) Stagnation of fluid-Dampness included the following clinical symptoms and signs: massive ascites making the abdomen like a drum, hypochondriac pain, edema in the lower extremities, lassitude, oliguria and loose stools, white and greasy tongue coating, fine pulse or weak pulse.

(d) Retention of Dampness due to stagnation of Qi included the following clinical symptoms and signs: abdominal distention causing a drum-like sound (the abdominal distention will ease after eructation or breaking wind), distending pain, poor appetite, thin and greasy tongue fur, edema in the lower extremities, oliguria, wiry pulse.

(e) Obstruction of collaterals by Blood stasis included the following clinical symptoms and signs: stabbing hypochondriac pain with an immovable site of pain, abdominal distention and subcutaneous varicose veins on the abdominal wall, ascites, hepatosplenomegaly, dim complexion, Liver palms, spider angioma, telangiectasis, dark red tongue or some ecchymosis and petechiae on the tongue, hypoglossal varicose veins, uneven pulse or thread pulse.

(f) Yin deficiency of Liver and Kidney included the following clinical symptoms and signs: low back pain or soreness and weakness of waist and knees, dull rib-side pain and becoming tired easily, dry eye, burning sensation of five centres, insomnia, tinnitus, deafness, dizziness, thirst, dry stools, brown urine, pale complexion, ascites, gingival bleeding, nasal bleeding, red tongue with no tongue coating, thready pulse or thready rapid pulse.

(g) Asthenic splenonephro-Yang included the following clinical symptoms and signs: abdominal distension that is aggravated in the afternoon, poor appetite, libido reduction, impotence, ejaculation praecox, chilly, lassitude, pale complexion, clear urine in large amounts and frequent urination at night, diarrhea that worsens after cold drink, ascites, edema in the lower extremities, pale tongue with slippery tongue fur, deep and thin pulse.

**Statistical analysis**

SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze data. Quantitative data are expressed as the mean ± standard deviation ( x ± s). Differences in measurement data were compared using the χ² test. P values < 0.05 were considered to denote significant differences.

**RESULTS**

The mean serum concentrations of zinc, iron, copper and magnesium according to the TCM symptom patterns of patients with CHB and HBV-induced cirrhosis are presented in Tables 1 and 2. In the CHB group, the mean concentration of magnesium in patients with toxic Heat flourishing was significantly lower than that of patients with Damp-Heat in the Liver and Gallbladder, and Liver depression and Spleen deficiency (P < 0.021). In the HBV-induced liver cirrhosis group, the mean concentration of zinc in patients with stagnation of fluid-Dampness was significantly lower than that in patients with obstruction of collaterals by Blood stasis (P < 0.034). The concentration of iron and copper

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**Table 1 Mean concentration of zinc, iron, copper and magnesium in CHB and chronic severe hepatitis B patients with different TCM patterns of symptoms ( x ± s )**

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Zinc</th>
<th>Iron</th>
<th>Copper</th>
<th>Magnesium [median (P_{25}-P_{75})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHLG</td>
<td>12.64±5.47</td>
<td>30.79±5.19</td>
<td>0.84±0.10’</td>
<td>10.35 (8.73-13.41)</td>
</tr>
<tr>
<td>LDSD</td>
<td>15.87±4.84</td>
<td>29.08±8.52</td>
<td>0.86±0.11’</td>
<td>12.12 (9.14-16.30)</td>
</tr>
<tr>
<td>ILS</td>
<td>16.20±5.19</td>
<td>28.30±5.65</td>
<td>0.79±0.10</td>
<td>18.51 (12.01-27.80)</td>
</tr>
<tr>
<td>RDH</td>
<td>10.45±1.08</td>
<td>29.25±8.56</td>
<td>0.80±0.05</td>
<td>11.87 (8.66-15.07)</td>
</tr>
<tr>
<td>THF</td>
<td>7.74±2.35</td>
<td>22.95±8.27</td>
<td>0.58±0.18</td>
<td>9.75 (8.57-10.92)</td>
</tr>
<tr>
<td>F/χ² value</td>
<td>1.97</td>
<td>0.65</td>
<td>3.37</td>
<td>5.61</td>
</tr>
<tr>
<td>P value</td>
<td>0.123</td>
<td>0.630</td>
<td>0.021</td>
<td>0.230</td>
</tr>
</tbody>
</table>

Notes: CHB: chronic hepatitis B; TCM: Traditional Chinese Medicine; DHLG: Damp-Heat in the Liver and Gallbladder; LDSD: Liver depression and Spleen deficiency; ILS: disharmony between the Liver and Stomach; RDH: retention of Damp-Heat; THF: toxic Heat flourishing. ’ and ‘’ indicate that the mean Mg concentration of patients with THF was significantly lower than that in those with DHLG and LDSD (P < 0.05).
showed little difference among the different TCM patterns of symptoms.

**DISCUSSION**

The liver function can objectively reflect the pathological state and has a close relationship with clinical symptoms. The clinical symptoms and signs are the external embodiment of pathogenic factors and physical interaction; hence, we can classify the clinical symptoms and signs into different TCM symptom patterns according to basic TCM diagnosis. The current study found a connection between the TCM symptom patterns and the mean concentrations of zinc and magnesium. This might help to explain the relationship between the pathogenesis transmission and TCM symptom patterns.

In patients with HBV-induced liver cirrhosis, the mean serum zinc concentration in those with stagnation of fluid-Dampness was significantly lower than that in those with static Blood blocking collaterals. Hence, we could infer that there was a correlation between the serum zinc concentration and the TCM symptom patterns of the patients with HBV-induced liver cirrhosis. Zinc is one of the components of many active enzymes, and it composes protein molecules, polysaccharide and nucleic acid; zinc can also protect the liver cells, promote the regeneration of liver cells, has anti-oxidant properties, and inhibits hepatic stellate cell proliferation and activation by the induction of metallothionein production. During the active stage of liver cirrhosis, liver function declines as hepatocytes are destroyed by the inflammatory response. As a result, a lot of zinc is lost and the intake decreases, meaning the serum concentration of zinc decreases with the development of liver cirrhosis. In decompensated cirrhosis, enzyme activity and protein synthesis decreases as the function of hepatocytes reduces, which leads to a decrease in plasma osmolality; this causes mass ascites, limb dropsy and oliguria, which corresponds to the differentiation factors of stagnation of fluid-Dampness. In our clinical observation, the pathological stage of static Blood blocking collaterals appears far earlier than that of stagnation of fluid-Dampness, and the patients with stagnation of fluid-Dampness also have pathological manifestations of Blood stasis; hence, the preferable interpretation might be that “unsmooth Blood circulation results in water retention”. The serum concentration of magnesium in CHB patients with the toxic Heat flourishing pattern was significantly lower than that of CHB patients with Damp-Heat in the Liver and Gallbladder and those with stagnation of Liver Qi with deficiency of Spleen. This suggests that the magnesium concentration had a close relationship with the TCM symptom patterns of liver diseases associated with HBV. Magnesium is a co-factor for many enzymes, and its most important function is to comprise cholinesterase, the Na+–K+-pump and DNA enzymes; it can also protect the liver cells through the inhibition of lipid peroxidation. So in the process of hepatitis, the more magnesium that is lost, the more serious the liver damage becomes. The patients also intake less magnesium because of disruption of digestive and absorptive functions. All of the above leads to a decline in serum magnesium concentration. We could therefore deduce that the level of magnesium in the CHB patients is affected by how severely the liver is damaged.

This indicates that patients manifesting the pattern of Toxic Heat flourishing would have more severe liver injury than those with the pattern of Damp-Heat in the Liver and Gallbladder and those with stagnation of Liver Qi with deficiency of Spleen. Our results agreed with this, as the group of patients with the toxic Heat flourishing pattern was composed of those with severe hepatitis and fulminant hepatitis, while the patients with the pattern of Damp-Heat in the Liver and Gallbladder and stagnation of Liver Qi with deficiency of

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Zinc</th>
<th>Iron</th>
<th>Copper</th>
<th>Magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQS</td>
<td>12.48±3.34</td>
<td>20.11±10.01</td>
<td>15.32±4.00</td>
<td>0.85±0.07</td>
</tr>
<tr>
<td>RDH</td>
<td>11.51±4.07</td>
<td>27.51±11.89</td>
<td>15.54±5.19</td>
<td>0.78±0.11</td>
</tr>
<tr>
<td>SFD</td>
<td>8.34±3.43</td>
<td>20.42±7.05</td>
<td>12.56±3.18</td>
<td>0.79±0.12</td>
</tr>
<tr>
<td>RDSQ</td>
<td>11.06±4.07</td>
<td>22.38±7.47</td>
<td>12.84±3.99</td>
<td>0.75±0.13</td>
</tr>
<tr>
<td>OCBS</td>
<td>16.26±4.75</td>
<td>20.83±9.82</td>
<td>14.39±2.53</td>
<td>0.84±0.09</td>
</tr>
<tr>
<td>VEE</td>
<td>8.64±3.37</td>
<td>20.33±11.71</td>
<td>14.37±2.64</td>
<td>0.81±0.05</td>
</tr>
<tr>
<td>Mean</td>
<td>12.48±3.34</td>
<td>20.11±10.01</td>
<td>15.32±4.00</td>
<td>0.85±0.07</td>
</tr>
<tr>
<td>SD</td>
<td>11.51±4.07</td>
<td>27.51±11.89</td>
<td>15.54±5.19</td>
<td>0.78±0.11</td>
</tr>
</tbody>
</table>

Spleen mostly manifested the mild and moderate symptoms of chronic hepatitis. Stagnation of Liver Qi is often the initial pathogenesis at the early stage of CHB. The Liver then restricts the Spleen, which results in Liver stagnation and Spleen deficiency characterized by the disturbance of the Spleen and Stomach; after a long time this causes Dampness to appear and produces the pattern of stagnation of Damp-Heat that would finally cause the toxic Heat flourishing pattern if it is allowed to remain. At the same time, the stagnation of Damp-Heat affects the dispersion function of the Liver, which leads to the stagnation of Qi and Blood. The pathological lesions produced by the factors of stagnation of Qi, Damp-Heat, Blood stasis and Heat-toxin become worse after being invaded by the HBV. As described above, the magnesium concentration decreases as the severity of liver damage increases. The results show that the level of magnesium in CHB patients with the toxic Heat flourishing pattern was significantly lower than that of those with the pattern of Damp-Heat in the Liver and Gallbladder and those with stagnation of Liver Qi with deficiency of Spleen. This might help to interpret the transmission of TCM pathogenesis of CHB.

Although the mean serum concentrations of iron and copper were not significantly different among the groups, these elements have a very close relationship with the development of liver cirrhosis. Iron can aggravate liver fibrosis by promoting lipid peroxidation, damaging DNA and proteins, and activating hepatic stellate cells into the muscle cells.11 A previous study also reported that excess copper damages the liver.12 The non-significant result in the current study might be related to the small sample size and the lack of a comparison group.

Our research has revealed that the serum concentrations of zinc and magnesium had an internal relationship with the TCM symptom patterns of CHB and HBV-induced liver cirrhosis. This might help to elucidate the pathogenesis of liver cirrhosis, and to understand the clinical significance of TCM symptom patterns in the diseases studied.

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