ORIGINAL ARTICLE

Chinese Medicine Syndrome Distribution of Chronic Hepatitis B Virus Carriers in Immunotolerant Phase∗

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ABSTRACT  Objective: To explore Chinese medicine (CM) syndrome distribution of chronic hepatitis B virus (HBV) carriers in Immunotolerant phase (ITP). Methods: One hundred and eighty-five chronic HBV carriers in ITP, seen in the Third Affiliated Hospital of Sun Yat-sen University from May 2009 to December 2010, were admitted in an observational study under the guidance of CM. Patients' CM symptoms and signs, demographics, liver biochemistry, and qualitative HBV DNA were recorded in the questionnaires. CM syndromes were then differentiated to 15 detailed types and analyzed by generalization. Lastly, the location, pathogenic factors and nature of the disease were also assessed. Results: When CM syndrome patterns were differentiated to 15 types, there were 27 (15%) no syndrome cases, 94 (50%) single syndrome cases and 64 (35%) compound syndromes cases. The main detailed syndromes included Liver (Gan)-qi depression (LQD), Kidney (Shen)-qi deficiency (KQD), Spleen (Pi)-qi deficiency (SQD) and Kidney-yang deficiency (KYAD). After CM syndromes generalized to five types, their frequency was Spleen-Kidney deficiency (SKD)>LQD>Inner dampness-heat retention (IDR)>Liver-Kidney deficiency (LKQD)>blood stasis blocking collateral (BSBC), SKD and LQD occupied 64%. The disease location included Liver, Gallbladder (Dan), Spleen, Stomach (Wei) and Kidney. The pathogenic factors were mainly qi stagnation, qi deficiency, yang deficiency, concurrently dampness-heat and blood stasis. The deficiency syndrome was more than excess syndrome in its nature. Conclusions: Most of chronic HBV carriers in ITP have their CM syndrome, and the most common types are SKAD, LQD. This study suggests that the natural history may be improved through breaking the state of immune tolerance or shorten the time of ITP by strengthening Spleen-Kidney and relieving Liver qi.

KEYWORDS  hepatitis B virus carrier, natural history, immune tolerance, Chinese medicine, syndrome differentiation

Because of the great burden in the management and treatment of diseases related to hepatitis B virus (HBV) for the government and infected individuals, chronic HBV infection is still a global health problem.1-10 Approximately 350–420 million people around the world are infected chronically by HBV.4,5 Carrier state, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) are the four main clinical outcomes caused by chronic infection.6-8 Whereas, most of the patients infected by HBV, especially residing in the Asia-Pacific region including China, are in the chronic HBV carrier state that is thought to be responsible for mother-to-child transmission.5,9-11

The history of chronic HBV infection includes four phases on the basis of the interaction between virus and host: immune tolerance, immune clearance, low or non-replication, and reactivation.12-13 Their clinic diagnoses are respectively chronic HBV carrier, hepatitis B e antigen (HBeAg) positive chronic hepatitis B (CHB), inactive hepatitis B surface antigen (HBsAg) carrier, and HBeAg negative CHB.

Though antiviral drugs are extensively used for treating CHB now, due to its immunotolerant state, there are still no agents recommended for chronic HBV carriers whose total numbers are greatly more than CHB. However, chronic HBV carriers have increased risk of developing cirrhosis and HCC.14 A recent study

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demonstrated that serious sequelae would come into being in 15% to 40% of them during their lifetime.\(^{(15)}\)

Chinese medicine (CM), characterized by syndrome differentiation and preventive treatment, has its features and advantages in the therapy of chronic HBV carriers.\(^{(16)}\) We know that syndrome differentiation is the essence of CM, and that recognizing its syndrome pattern is the key of preventing and treating the disease. Therefore, if augmenting the dominant role of CM in it, we must know the distribution of the CM syndrome pattern of chronic HBV carrier in ITP.

Studies\(^{(17-20)}\) on the CM syndrome pattern distribution of CHB in the phases of immune clearance and reactivation have been developed widely, and the standard of syndrome differentiation is already formulated,\(^{(18)}\) but those of chronic HBV carriers have not been studied. Due to their different phases in natural history, chronic HBV carriers and CHB must have their own CM syndrome according to the ever-moving point of CM. Therefore, the CM syndrome pattern of chronic HBV carriers in ITP is still unknown. Hence, the aim of this study was to explore the CM syndrome distribution of chronic HBV carriers in ITP.

**METHODS**

**Patients**

This was an observational study under the guidance of CM. A total of 185 chronic HBV carriers in ITP in the Third Affiliated Hospital of Sun Yat-sen University from May 2009 to December 2010, were admitted in this study according to the following diagnostic and exclusive criteria. Their domicile province included Guangdong, Hunan, Hubei, Shandong, Anhui. Their demographics, liver biochemistries, HBeAg status and qualitative HBV DNA were summarized in Table 1. Liver biopsy was taken in 41 cases and their histological activity indices (HAI) were recorded in Table 2 based on grade (G) of inflammation and stage (S) of fibrosis.

Chronic HBV carriers were diagnosed in accordance to the Chinese Guideline of Prevention and Treatment for CHB published in 2005.\(^{(21)}\) The ITP was defined as serum HBeAg positive, high viral load, alanine amino-transferase (ALT) \(<2 \times \) upper limit normal (ULN).\(^{(22)}\)

The following patients were excluded: (1)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number or median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Case, male/female)</td>
<td>104/81</td>
</tr>
<tr>
<td>Age (Years, median, min.-max.)</td>
<td>29 (4–62)</td>
</tr>
<tr>
<td>Serum ALT (IU/L, median, 10%–90% CI)</td>
<td>27 (13–40)</td>
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<tr>
<td>Serum AST (IU/mL, median, 10%–90% CI)</td>
<td>24 (15–39)</td>
</tr>
<tr>
<td>Serum HBeAg (Case, positive/negative)</td>
<td>185/0</td>
</tr>
<tr>
<td>Serum HBV-DNA (log10 copies/mL, median, 10%–90% CI)</td>
<td>8.35 (7.36–8.96)</td>
</tr>
<tr>
<td>Ways of HBV acquisition</td>
<td></td>
</tr>
<tr>
<td>Mother-to-child (Case, %)</td>
<td>34 (18.4%)</td>
</tr>
<tr>
<td>Unclear (Case, %)</td>
<td>151 (81.6%)</td>
</tr>
</tbody>
</table>

**Table 1. General Characteristics of Chronic HBV Carriers in ITP (185 cases)**

Superinfected with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus (HIV). (2) Co-existence with alcoholic, metabolic or auto-immune liver disease. (3) Treated by antiviral agents. (4) Having serious heart, lung or kidney diseases. (5) Having a history of mental illness.

**Observational Items**

Selected patients' CM symptoms and signs, demographics, serum liver biochemistries (ALT, AST), serum HBV markers and serum qualitative HBV DNA were recorded in the questionnaires.

**Assays of HBV Markers and Viral Load**

Serologic HBV markers were measured by enzyme linked immunosorbent assay. Qualitative HBV DNA were detected by fluorescence quantitative polymerase chain reaction (PCR) assay (Da-An Gene, Sun Yat-Sen University, China).

**Standards and Performance of CM Syndrome Differentiation**

This study was designed under the guidance of CM and from observational study. Firstly, all the above patients' data were investigated or measured and then recorded. After that, CM syndromes, locations of