Natural course following the onset of cirrhosis in patients with chronic hepatitis B: a long-term follow-up study

Yi-Cheng Chen · Chia-Ming Chu · Chau-Ting Yeh · Yun-Fan Liaw

Abstract

Purpose To elucidate the long-term natural course following the onset of cirrhosis in patients with chronic hepatitis B.

Methods Ninety-three patients with chronic hepatitis B who had developed cirrhosis during regular follow-up were included in this long-term follow-up study. At the time of cirrhosis detection, 30% of the patients were seropositive for hepatitis B e antigen (HBeAg) and 73% had a HBV-DNA level >10^{4} copies/ml. Follow-up studies included liver biochemistry, viral markers, α-fetoprotein and ultrasonography every 3–6 months.

Results During a mean follow-up period of 102 ± 60 (12–246; median 97) months, 32 patients (34.4%) experienced 55 episodes of hepatitis flare (7.0%/year), 15 (53.6%) of 28 HBeAg-positive patients seroconverted to anti-HBe (6.3%/yr) and 12 (12.9%) lost HBsAg (1.5%/year). Overall disease progression was observed in 25 (26.9%, 3.2%/year) patients: 12 (12.9%, 1.5%/year) hepatic decompensation, 21 (22.6%, 2.7%/year) hepatocellular carcinoma and 11 (11.8%, 1.4%/year) died. Multivariate analysis showed that age at onset of cirrhosis \( P = 0.015 \) and persistent HBeAg seropositivity \( P = 0.019 \) were the independent factors for overall disease progression.

Conclusions These results suggest that patients with older age at onset of cirrhosis and persistent HBeAg seropositivity following the onset of cirrhosis were independent factors for the disease progression in the first 10-year after the development of cirrhosis in patients with chronic hepatitis B.

Keywords Hepatitis flare · Hepatic decompensation · Hepatocellular carcinoma · HBeAg seroconversion · HBsAg seroconversion

Abbreviations HBV Hepatitis B virus · HCC Hepatocellular carcinoma · HBeAg Hepatitis e antigen · HBsAg Hepatitis B surface antigen · HCV Hepatitis C virus · HDV Hepatitis D virus · AFP α-Fetoprotein · ALT Alanine aminotransferase · ULN Upper limit of normal · PCR Polymerase chain reaction · PT Prothrombin time

Introduction

Hepatitis B virus (HBV) affects 350–400 million people chronically worldwide [1]. Chronic HBV infection may
lead to cirrhosis or hepatocellular carcinoma (HCC), or both in some patients [2–5]. Earlier studies showed that age, acute exacerbation, and functional status are contributing factors of outcomes and mortality in patients with HBV related cirrhosis [6–9]. However, most of the earlier studies examined patients with cirrhosis of unknown onset and the follow-up duration was relatively short. Therefore, the natural course following the onset of cirrhosis is not clearly known. We therefore conducted this long-term follow-up study.

Materials and methods

Patients

Thousands of patients with chronic HBV infection, or those seropositive for hepatitis B surface antigen (HBsAg) ≥6 months, have been followed up periodically since 1970s in our liver unit, as described earlier [2–4]. A total of 1,292 patients were histologically confirmed to have chronic hepatitis B and no evidence of liver cirrhosis before the end of 1999. After histological diagnosis, they were regularly followed up and 190 patients were found to have developed cirrhosis subsequently. Excluding 27 patients with hepatitis C virus (HCV) or hepatitis D virus (HDV) concurrent infection, 58 patients who had received antiviral therapy and 12 patients who were followed up for less than 1 year, the remaining 93 patients with HBV infection alone were included in this study. These patients included 80 males (86%) and 13 females (14%) with a mean age of 43.6 ± 10.4 (24–69, median 40.8 year) at the onset of cirrhosis. Upon diagnosis of cirrhosis, 65 (70%) were hepatitis B e antigen (HBeAg) negative and 28 (30%) were HBeAg positive. Sixty-five (73%) of 89 patients assayed showed a serum HBV-DNA level >10^4 copies/ml (Table 1).

Follow-up

Since liver cirrhosis was detected during regular periodic follow-up, the time of detection is identical or very close to the onset of cirrhosis [2]. Following detection of cirrhosis, the patients were followed up every 3–6 months, or more frequently if clinically indicated, for at least 12 months after the diagnosis of cirrhosis. Follow-up studies included clinical evaluation, liver biochemical, virological markers and α-fetoprotein (AFP). The ultrasonography was also performed for the surveillance of HCC. Endoscopic examination was done at least once for evaluation of esophageal/gastric varices and was used to confirm variceal bleeding whenever upper gastrointestinal bleeding happened. The follow-up period following onset of cirrhosis ranged from 12 to 246 months (median 97.3 months; mean 102 ± 60 months) (Table 2).

Methods

Liver biochemical tests and blood cell counts were performed using automatic analyzer. Episodes with alanine aminotransferase (ALT) elevation by twofold of the baseline level and over five times the upper limit of normal (ULN, 36 U/L) were considered as “hepatitis flares” [10–13]. Virological markers including hepatitis B surface antigen (HBsAg), HBeAg, anti-HBe and anti-HDV were assayed using commercially

<p>| Table 1: The demographic data at the onset of cirrhosis in patients with chronic hepatitis B |
|-----------------------------------------------|------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Age at onset (years)</th>
<th>HBeAg (–) (n = 65)</th>
<th>HBeAg (+) (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>43.6 ± 10.4 (24–69)</td>
<td>44.8 ± 10.3 (28–68)</td>
<td>40.6 ± 10.3 (24–69)</td>
<td>0.072</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBV DNA (copies/ml)^b</th>
<th>HBeAg (–) (n = 65)</th>
<th>HBeAg (+) (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300</td>
<td>15</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>300–9,999</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>10,000–99,999</td>
<td>12</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>≥100,000</td>
<td>53</td>
<td>32</td>
<td>21</td>
</tr>
</tbody>
</table>

^a Data as mean ± SD (range)  
^b Excluding four patients with missing data

<p>| Table 2: The outcomes following the onset of cirrhosis in patients with chronic hepatitis B |
|-----------------------------------------------|------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Follow-up (months)^a</th>
<th>HBeAg (–) (n = 65)</th>
<th>HBeAg (+) (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>102 ± 60 (12–246)</td>
<td>101.9 ± 60.1 (14–246)</td>
<td>102.2 ± 59.9 (12–234)</td>
<td>0.984</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBeAg seroconversion^b</th>
<th>Hepatitis flare</th>
<th>Case^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 (34.4)</td>
<td>24 (36.9)</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Episodes</td>
<td>55</td>
<td>43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBsAg clearance^b</th>
<th>Decompensation^b</th>
<th>HCC^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 (12.9)</td>
<td>11 (16.9)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>12 (12.9)</td>
<td>7 (10.8)</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>21 (22.6)</td>
<td>12 (18.5)</td>
<td>9 (32.1)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Liver-related death^b</th>
<th>Disease progression^b</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (11.8)</td>
<td>6 (9.2)</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>25 (26.9)</td>
<td>15 (23.1)</td>
<td>10 (35.7)</td>
</tr>
</tbody>
</table>

* HCC: hepatocellular carcinoma; disease progression: hepatic decompensation or HCC
^a Mean ± SD (range)  
^b No (%)