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# Original Article

# Clinical Characteristics and Treatment for Patients with Occult Chronic Hepatitis B

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**Objective** To observe the clinical manifestations and assess direct antiviral effect for patients with occult hepatitis B in China.

**Methods** The study includes 15 patients with occult hepatitis B and their medical history, family history, first-diagnosis time, confirmed-diagnosis time, laboratory report, anti-viral therapy and outcomes were analyzed.

**Results** The average age of the patients is 38.67-year old (6 males and 9 females), 2 with acute hepatitis B (2/15, 13.3%), 13 with no hepatitis history (13/15, 86.6%), 8 with family history (8/15, 53.3%), 6 with no family history (6/15, 40%), 1 with unknown family history (1/15, 6.6%). Eight patients were treated with entecavir (0.5 mg/day, taken orally), with effective results and steady conditions; 3 patients were treated with lamivudine (0.1 g/day, taken orally), 2 of them were prescribed to take adefovir dipivoxil additionally due to drug-resistance, the other one was treated with lamivudine continuously without drug-resistance; 4 cases refused anti-viral therapy. One patient's condition remained steady, 1 patient died of cirrhosis with portal hypertension and liver failure 5 years after first-diagnosis, 1 patient progressed to hepatocellular carcinoma and accepted surgery operation treatment 5 years after first-diagnosis, the other 1 patient progressed to compensatory cirrhosis 2 years after first-diagnosis and is steady from then, which indicates that occult chronic hepatitis B can progress to cirrhosis and hepatocellular carcinoma without therapy in time.

**Conclusions** The clinical characteristics of 15 cases with occult chronic hepatitis B showed that these patients with short latency, younger age when being-struck, and light damage to liver function. The efficacy and drug-resistance of nucleos(t)ide-analogue (entecavir, lamivudine, adefovir dipivoxil) in treatment of patients with occult chronic hepatitis B are similar to chronic hepatitis B.

**Key words**: Occult; Chronic hepatitis B; Clinical course; Treatment

Occult hepatitis B virus (HBV) infection can be defined as the long persistence of virus in liver tissue (in serum of some cases ) of individuals with HBV surface antigen (HBsAg) negative.[1] This infectious situation may occur in the population with anti-HBc and/or anti-HBs positive and all HBV serum marker negative.[2] Clinically, pathogenesis of 5%-10% patients with chronic hepatic diseases can not be confirmed just depending on clinical manifestation, routine biochemical and serum detection. Some patients were diagnosed definitely as occult HBV infection by liver needle biopsy and/or serum HBV DNA detection.[3,4] Occult HBV infection can cause liver diseases with unknown reasons, even hepatocellular carcinoma.[5] Additionally, patients with occult HBV infection can be the sources of HBV transmition. HBV infection is common in China, with HBsAg positive rate reaching 7.18% in population across the country,[6,7] and clinical observation reports on chronic hepatitis B due to occult HBV infection are quite rare. Also, data on antiviral therapy in patients with occult HBV infection are few. The likelihood of benefit on antiviral therapy is low as most patients with occult HBV infection have very low levels of HBV DNA. For patients with persistently high serum HBV DNA levels and absence of other causes of liver disease, antiviral therapy may be considered. Therefore, the goals of our present study were: (1) to investigate the clinical manifestations of patients with occult hepatitis B in China; (2) to assess the direct antiviral effect reflected by serum HBV DNA reduction.

## PATIENTS AND METHODS

All patients were either hospitalized or out-patients at Dalian Sixth People Hospital, Dalian City, Liaoning Province, over the past six years. A total of 15 patients with occult HBV infection were included in this study. The diagnosis of occult HBV infection was confirmed according to the criteria of AASLD. Other possible causes of liver diseases including hepatitis C,

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**Table 1. Base-line characteristics of the 15 patients with occult hepatitis B**

| No. | Sexes | Age (years) | History | Family history | Time of first-treatment | Results of detection before first-treatment |
|---|---|---|---|---|---|---|
| 1 | Male | 32 | No hepatitis history | Mother HBsAg (+) | January 2003 | Anti-HBs (+), anti-HBc (+), HBV DNA (+) |
| 2 | Male | 28 | Acute hepatitis B 1 year ago | None | May 2004 | Anti-HBs (+),anti-HBc (+), anti-HBe (+), HBV DNA (+) |
| 3 | Female | 36 | No hepatitis history | Mother HBsAg (+) | September 2004 | Anti-HBs (+), anti-HBc (+), HBV DNA (+) |
| 4 | Male | 42 | No hepatitis history | Mother HBsAg (+) | April 2005 | Anti-HBs (+), anti-HBc (+), HBV DNA (+) |
| 5 | Female | 48 | No hepatitis history | None | June 2005 | Anti-HBs (+), anti-HBc (+), anti-HBe (+), HBV DNA (+) |
| 6 | Female | 45 | Acute hepatitis B 2 years ago | None | September 2005 | Anti-HBs (-), anti-HBc (+), HBV DNA (+) |
| 7 | Female | 43 | No hepatitis history | Unknown | April 2006 | Anti-HBs (+), nti-HBc (+), HBV DNA (+) |
| 8 | Male | 29 | No hepatitis history | Mother HBsAg (+) | August 2006 | Anti-HBs (+), anti-HBc (+), HBV DNA (+) |
| 9 | Female | 35 | No hepatitis history | Mother HBsAg (+) | September 2006 | Anti-HBs (+), anti-HBc (+), HBV DNA (+) |
| 10 | Female | 39 | No hepatitis history | None | March 2007 | Anti-HBs (-), anti-HBc (+), HBV DNA (+) |
| 11 | Female | 37 | No hepatitis history | None | August 2007 | Anti-HBs (-), anti-HBe(+), HBV DNA (+) |
| 12 | Female | 46 | No hepatitis history | Mother HBsAg (+) | May 2008 | HBV DNA (+) |
| 13 | Male | 35 | No hepatitis history | None | February 2005 | Anti-HBs (-), anti-HBe (+), HBV DNA (+) |
| 14 | Male | 37 | No hepatitis history | Mother HBsAg (+) | January 2008 | Anti-HBs (+), anti-HBc (+), HBV DNA (+) |
| 15 | Female | 48 | No hepatitis history | Mother HBsAg (+) | May 2008 | Anti-HBs(+), anti-HBe (+), anti-HBc (+), HBV DNA (+) |

significant alcohol intake (> 40 g/day), the consumption of any medication that might be associated with liver injury were excluded from this study. The clinical and biological parameters including HBV viral load of all patients were assessed by HBV transcription-mediated amplification method. Totally, 13 out of 15 occult hepatitis B patients received antiviral treatment. The baseline clinical data of the patients are summarized in Table 1.

## RESULTS

Total of 15 patients were diagnosed as occult hepatitis B, with the clinical features shown in Table 1, and their average age was 38.67 years old, 6 were male and 9 female, 2 with acute hepatitis B (2/15, 13.3%), 13 with hepatitis history (13/15, 86.6%), 8 with family history (8/15, 53.3%), 6 with no family history (6/15, 40%), 1 with unknown family history (1/15, 6.6%). The first treatment period is from January 2003 to May 2008. The results before first treatment: 15 cases with HBV DNA (+) , 7 cases with anti-HBs (+) and anti-HBc (+) (7/15, 46.6%), 3 cases with anti-HBs (+), anti-HBc (+) and anti-HBe (+) (3/15, 20%), 2 cases with anti-HBs (-) and anti-HBc (+) (2/15, 13.3%), 2 cases with anti-HBs (-) and anti-HBe (+) (2/15, 13.3%), 1 case with anti-HBs (-), anti-HBc (-) and anti-HBe (-) (1/15, 6.6%). The confirmed diagnosis period is from February 2005 to May 2010, all 15 patients occurred right up-abdomen discomfort, fatigue, and anorexia, etc. Liver function: ALT 50 - 300 U/L, HBV DNA $8.0 \times 10^2$ - $5.3 \times 10^7$ IU/ml; liver injury caused by other viruses or nonvirus factors were excluded for all patients, and occult chronic hepatitis B were confirmed in accordance with the diagnosis criteria.

Totally, 8 patients were treated with entecavir (0.5 mg/day, taken orally) and the treatment effect is steady; 3 patients were treated with lamivudine (0.1 g/day, taken orally), 4 refused to receive anti-viral therapy. As shown in table 2, entacavir treatment resulted in stronger suppression of HBV replication, reflected by significant reduction in serum HBV DNA levels. And 2 were prescribed to take adefovir dipivoxil additionally due to drug-resistance, 1 patient was treated with lamivudine continuously without drug-resistance. One patient's condition remained steady, 1 patient died of cirrhosis with portal hypertension and hepatic failure 5 years after first-diagnosis, 1 patient progressed to hepatocellular carcinoma and accepted surgery operation and still alive 5 years after first-diagnosis, 1 patient progressed to compensatory cirrhosis 2 years after first-diagnosis and is steady from then.

**Table 2. Diagnosis, treatment and outcomes of the 15 patients with occult hepatitis B**

| No. | Time of comfirmed diagnosis | ALT (U/L) | HBV DNA (IU/ml) | Clinical diagnosis | Anti-viral therapy | Treatment outcomes |
|---|---|---|---|---|---|---|
| 1 | November 2009 | 60 | $2.0 \times 10^3$ | Occult chronic hepatitis B | Entecavir (0.5 mg/day, taken orally) | Viral response |
| 2 | August 2009 | 80 | $2.0 \times 10^3$ | Occult chronic hepatitis B | None | Clinical follow-up |
| 3 | February 2006 | 50 | $6.0 \times 10^5$ | Occult chronic hepatitis B | Lamivudine (0.1 g/day), adefovir dipivoxil (10 mg/day) added after 2 years | Viral response |
| 4 | December 2007 | 270 | $7.0 \times 10^3$ | Occult chronic hepatitis B | None | Died of cirrhosis with portal hypertension and liver failure in December 2010 |
| 5 | March 2010 | 78 | $5.0 \times 10^3$ | Occult chronic hepatitis B | None | Surgery operation due to liver cancer in May 2010 and with clinical follow-up |
| 6 | August 2008 | 75 | $3.0 \times 10^3$ | Occult chronic hepatitis B | Lamivudine (0.1 g/day) | Viral response |
| 7 | May 2009 | 230 | $2.6 \times 10^4$ | Occult chronic hepatitis B | Entecavir (0.5 mg/day, taken orally) | Viral response |
| 8 | January 2009 | 120 | $5.0 \times 10^4$ | Occult chronic hepatitis B | Entecavir (0.5 mg/day, taken orally) | Viral response |
| 9 | May 2009 | 80 | $2.0 \times 10^5$ | Occult chronic hepatitis B | Entecavir (0.5mg/day, taken orally) | Viral response |
| 10 | October 2009 | 120 | $7.0 \times 10^5$ | Occult chronic hepatitis B | Entecavir (0.5 mg/day, taken orally) | Viral response |
| 11 | May 2009 | 160 | $5.0 \times 10^3$ | Occult chronic hepatitis B | Entecavir (0.5 mg/day, taken orally) | Viral response |
| 12 | September 2008 | 107 | $8.0 \times 10^2$ | Occult chronic hepatitis B | None | Diagnosed as compensatory cirrhosis in February 2010 and with clinical follow-up |
| 13 | September 2008 | 300 | $5.3 \times 10^7$ | Occult chronic hepatitis B | Lamivudine (0.1 g/day), adefovir dipivoxil (10 mg/day) added after 2 years | Viral response |
| 14 | May 2010 | 270 | $3.0 \times 10^4$ | Occult chronic hepatitis B | Entecavir (0.5 mg/day, taken orally) | Viral response |
| 15 | October 2010 | 180 | $6.0 \times 10^4$ | Occult chronic hepatitis B | Entecavir (0.5 mg/day, taken orally) | Viral response |

## DISCUSSION

Occult HBV infection was first reported in 1970s. Along with the development of molecular biology in recent 10 years, occult HBV infection has been appreciated generally and demonstrated clearly, which is defined to the situation that serum HBsAg is negative and serum and/or liver biopsy tissue HBV DNA is positive consistently. There are many evidences indicated that occult HBV infection exists objectively, with infectiousness and pathogenicity, and has significant importance in pathogeny diagnosis of hepatic disease, safety of blood donation, HBV detection of recipient of organ transplantation, etc. The pathogenesis of occult HBV infection may be correalted with gene mutation, low level of HBV replication, gene integration, HBsAg expression and excretion inhibition, etc.[8-10] Some researchers considered that HBV DNA could exist for a long time as occult infection after self-healing of acute hepatitis B.[11] But morbidity of occult hepatitis B is low in chronic hepatitis B epidemic area.[11] HBV DNA in serum of a significant number of patients with anti-HBc (+) were detectable. Chronic hepatitis C patients had a high prevalence of occult HBV infection.[12] Although HBV replication is at a low level, it still can expedite liver disease progression and lead to hepatic fibrosis, cirrhosis or liver cancer.[10,13] And patients with HBsAg positive may progress into liver cancer although with no cirrhosis.[14] When the immune system is inhibited, HBV in occult infection situation would replicate again, and serum markers such as HBsAg may appear and eventually progress into typically chronic hepatitis B.

Occult hepatitis B is defined that serum HBsAg is negative and HBV DNA in serum and/or liver biopsy tissue is positive, and patients with clinical manifestation of chronic hepatitis B. Except HBV DNA is positive, anti-HBs, anti-HBe and/or anti-HBc may

be positive in patients' serum. Serum markers in about 20% patients with occult chronic hepatitis B were negative, and liver injury caused by other viruses and non-virus factors should be excluded.[15]

The clinical characteristics of 15 cases with occult chronic hepatitis B showed that latency was short, age of being struck was young and damage to liver function was light. Serum HBV DNA level was from $8.0 \times 10^2$ to $5.3 \times 10^7$ IU/ml. And it could be concluded that the occurrence of occult chronic hepatitis B is not related to the history of acute hepatitis B and family history of HBV infection in all 15 cases. No confirmed treatment strategy for occult chronic hepatitis B at home or abroad is available at present, and interferon usage is relatively strict and with more side-effects. Among the 13 cases who were treated with anti-viral drugs either entecavir or lamivudine or adefovir dipivoxil, especially the 8 patients treated with entecavir, no drug-resistance or viral mutation occurred, while 3 cases progressed to cirrhosis or liver cancer among the 4 patients without nucleos(t)ide analogue treatment, which implies that etiologic treatment is urgent and necessary for patients with occult chronic hepatitis B, and the efficacy and drug-resistance of nucleos(t)ide-analogue in treatment of these patients are similar to that of patients with chronic hepatitis B. Due to the limited cases and short observation period, the pathophysiological procession from occult HBV infection to occult chronic hepatitis B has not been reported in details, which needs further observations and researches to observe whether the clinical course is similar to that of chronic hepatitis B.

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