Effect of seasonal variation on the clinical course of chronic hepatitis B

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**Background.** Seasonal variation in immunity has been found in healthy individuals and in association with some diseases. It is still unknown whether seasonal variation affects the clinical course of chronic hepatitis B. Our aim in this study was to explore the effect of seasonal variation on the clinical course of chronic hepatitis B.

**Methods.** The flare and remission time of chronic hepatitis B were observed in patients with hepatitis B virus (HBV) infection. All patients enrolled were followed up at least every 3 months for a mean follow-up time of 24.0 (range, 12–60) months. Seasonal decomposition was employed to analyze the relationship between seasonal variation and flares, remission, and hepatitis B e antigen (HBeAg) seroconversion in chronic hepatitis B patients during follow-up.

**Results.** A total of 2238 patients were observed in our study. Flare and HBeAg seroconversion were seldom seen in 1076 patients (48.08%) with alanine aminotransferase (ALT) levels of less than 2.0 × upper limit of normal (ULN) during follow-up (mean, 36 months). The remaining 1162 patients (51.92%) (766, HBeAg positive; 387 anti-HBeAg positive; 9 negative for both HBeAg and anti-HBeAg) with ALT levels ≥2.0 × ULN were followed longitudinally for 12 months to judge flare, remission, and HBeAg seroconversion. Flare, remission, and HBeAg seroconversion in patients with ALT levels ≥2.0 × ULN showed clear seasonal patterns (P < 0.001), with high peaks during spring, summer, and summer, respectively. An autocorrelation correlogram showed that flares, remission, and HBeAg seroconversion occurred with distinct periodicity in winter, spring, summer, and autumn.

**Conclusions.** Seasonal variation might affect the clinical course of chronic hepatitis B. The role of seasonal triggering factors should be further investigated.

**Key words:** chronic hepatitis B, seasonal variation

**Introduction**

Chronic hepatitis B virus (HBV) infection is a serious clinical problem because of its worldwide distribution and possible adverse sequels. Hepatitis flares occur frequently in patients with chronic HBV infection during the natural course of chronic HBV infection, sometimes complicated by decompensation or cirrhosis, and hepatocellular carcinoma (HCC) may develop.

Chronic HBV infection involves dynamic interaction among HBV, hepatocytes, and the immune system of the host. Any factors that may affect any of these can affect the clinical course of chronic hepatitis B.

Seasonal variation has been documented in the exacerbation and attributable mortality of a number of illnesses, including some liver diseases. Whether similar trends exist in chronic hepatitis B is not definitively known. This prospective clinical study was performed in the Liver Diseases Center of Traditional Chinese Medicine (TCM) of The First Affiliated Hospital of Sun Yat-Sen University and Liver Diseases Center of TCM Hospital of FuShan. We observed the effect of seasonal variation on the clinical course of chronic hepatitis B patients from January 1996 to December 2004.

**Materials and methods**

**Patients**

The study population consisted of all patients with chronic hepatitis B who visited our Liver Diseases Center from January 1996 to December 2004. This prospective clinical study was approved by the local ethics committee, and each participant provided written consent.
Patients had all been hepatitis B surface antigen (HBsAg)-positive for at least 6 months when they were entered into the trial. Patients were excluded from the study if they (1) had complications with hepatitis C or other hepatic viral infection, (2) had possible autoimmune, drug, or alcoholic hepatitis, or cirrhosis, (3) had received anti-HBV therapy (lamivudine, interferon, thymosin, or other antiviral therapy), (4) had been followed up for less than 12 months, (5) were pregnant or breastfeeding, or (6) had severe cardiovascular, renal, or hematopoietic system complications, or mental disease.

Identification of flares or acute exacerbation
A flare or acute exacerbation was defined as an abrupt elevation of the serum alanine aminotransferase (ALT) level to more than 4 times the upper limit of normal (ULN) and 2 times the baseline value after excluding other common causes of ALT elevation, such as other viral hepatitis infection, drug-induced hepatitis, alcoholic hepatitis, or steatohepatitis.

Assessment of remission
In hepatitis B e antigen (HBeAg)-positive patients, remission was assessed by the loss of serum HBeAg, serum HBV-DNA decreased to \(<5 \text{ log copies/ml}\), and serum levels of ALT and aspartate aminotransferase (AST) restored to normal. In HBeAg-negative patients, remission was assessed by serum HBV-DNA decreased to \(<4 \text{ log copies/ml}\), and serum levels of ALT and AST restored to normal.

Exposure variables
The primary exposure variable for this study was season of the year. We arbitrarily defined winter as December, January, and February; spring as March, April, and May; summer as June, July, and August; and autumn as September, October, and November.

If ALT increased over two seasons, the flare season was identified by the time at which it first exceeded \(4 \times \text{ULN}\).

Laboratory investigations
Serum transaminase, albumin, bilirubin, amylase, and prothrombin time were measured by standard laboratory procedures. HBsAg, HBeAg, anti-HBeAg, anti-HBsAg, anti-hepatitis B core antigen, anti-hepatitis C virus, anti-hepatitis D virus, and anti-human immunodeficiency virus were detected by enzyme immunoassay. Quantitation of HBV-DNA was carried out with a commercially available quantitative polymerase chain reaction (PCR) assay (Da AN Gene Diagnostic Center of Sun Yat-Sen University, Guangzhou, China).

Methods of follow-up
A complete history was taken and a physical examination of all patients was performed during the first clinical visit. Blood was taken for liver biochemistry, \(\alpha\)-fetoprotein, and HBV serological markers during the first visit and every subsequent visit, scheduled at intervals of 1–3 months. For example, patients whose ALT was \(<2 \times \text{ULN}\) were followed up every 3 months, while those whose ALT was \(\geq 2 \times \text{ULN}\) were followed up monthly or bimonthly, or more frequently whenever indicated. HBV-DNA levels were examined only once each season.

Patients were divided into two groups according to their ALT levels: those whose ALT levels were \(<2 \times \text{ULN}\) were allocated to group A, and those whose ALT levels were \(\geq 2 \times \text{ULN}\) were allocated to group B. Once the ALT levels of patients in group A were found to be \(\geq 2 \times \text{ULN}\), they were moved to group B for closer observation.

Those patients who had clinical symptoms and with ALT \(\geq 2 \times \text{ULN}\) were treated with traditional Chinese medicinal herbs or other palliative therapies during the follow-up period, and those who showed a tendency to progress to severe liver injury were treated by a combination of methods to improve hepatic function. Use of Chinese herbs such as Fructus Schisandrae, Herba Sedi Sarmentosi, and Radix Sophorae Flavescentis, as well as ingredients extracted from Chinese herbs (such as deoxyschizandrin, monoammonium glycyrrhizinate, biphenyldicarboxylate, and oxymatrine), known to have a strong effect on ALT levels were avoided in our study. Moreover, the use of interferon, nucleoside analog, or other antiviral therapies was also avoided during the observation period of our study.

Statistical analysis
All statistics were performed with SPSS 12.0 for Windows (Chicago, IL, USA). Seasonal multiplicative decomposition was used to analyze flares, remission, and HBeAg seroconversion in chronic hepatitis B patients during the four seasons. In the multiplicative method, the indices average 100. Autocorrelation correlograms were used to show whether flares, remission, or HBeAg seroconversion in chronic hepatitis B patients displayed periodicity during the four seasons.

Results
Baseline characteristics of 2238 patients with chronic HBV infection are listed in Table 1; these patients were