Background: Chronic infection with hepatitis B virus (HBV) causes a spectrum of diseases ranging from asymptomatic infective state to cirrhosis and hepatocellular carcinoma. The asymptomatic state has highly variable characteristics. Methods: Sixty-one incidentally detected asymptomatic HBsAg-positive subjects (IDAHS), in whom HBsAg positivity persisted for >6 months, were studied for liver biochemistry, HBeAg, anti HBe and HBV DNA levels (in HBeAg-negative subjects). Liver biopsy was done in 29 subjects and scored for histological activity index (HAI) and fibrosis using modified Knodell score. Results: Thirteen (21%) subjects were HBeAg positive. The remaining 48 (79%) were positive for anti HBe, with HBV DNA level of >10^5 copies/mL in 15 (31.2%). Transaminase elevation was more frequent in HBeAg-positive subjects (69%; p<0.05) and in HBV DNA-positive (93%) than in non-replicative (27%) infection. Seroconverted (anti HBe-positive) individuals were a decade older than HBeAg-positive ones and most (93.7%) of them were >20 years of age. Fifteen of 29 (51.3%) had HAI >3, more frequently in those with raised ALT (68.4%; p<0.05) than with normal ALT (20%), but there was no difference in relation to HBeAg status. Conclusions: Seroconversion to anti HBe was noted in individuals aged 20 years or more. Ongoing liver disease was noted in approximately half of IDAHS, suggesting that a considerable proportion of IDAHS have active infection. In HBeAg-negative subjects, transaminase estimation may be sufficient in planning therapy. [Indian J Gastroenterol 2007;26:159-161]

Hepatitis B virus (HBV) infection has a dynamic natural history.1,2 HBeAg-negative state, a favorable phase in the natural history, can reconvert to HBeAg-positive state in a lifetime in 20%-30% of cases,2 due to one or more reactivations, leading to progressive liver disease.3 Although on presentation incidentally-detected asymptomatic HBsAg-positive subjects (IDAHS) appear healthy, varying proportions have evidence of liver disease on investigation.5,6

In studies from the West, HBeAg positivity has been noted in 4%-41% in IDAHS,3,6,7 with ALT elevation in two-thirds6 and HAI >3 in one-fourth of subjects.7 Although in studies from India HBeAg positivity was similar (9%-45%),5,8 three-fourths had raised ALT and 70% had abnormal liver histology (HAI >3). Anti HBe positivity in IDAHS in studies from the West has been 58%-96%,3,6,7 with infrequent (2%-20%) hepatic damage. Among anti HBe-positive subjects, HBV DNA positivity was 14%7 and raised ALT in 17%;6 studies from Asia report high HBV DNA positivity (17%-60%).4,5,9

Methods

Between December 2003 and May 2005, 75 IDAHS were seen at the Gastroenterology OPD of our institute; 61 of these (mean [SD] age 27.9 [10] y [range 6-60 y]; 48 men) fulfilled our inclusion and exclusion criteria. The ethics committee of the hospital approved the study. These subjects were detected positive on routine checkup by referring physicians for immigration or insurance purpose in 30 (49%); and before delivery, before surgery, or in the blood bank in 4 (6.5%) each; the remaining 19 (31%) were household contacts of patients with HBV-related chronic liver disease.

Subjects who had HBsAg positivity on two occasions more than 6 months apart and reconfirmed prior to enrollment; those with no symptom of liver disease; and those who consented for liver biopsy were included. Patients with history of chronic liver disease or decompensation of liver function in the past, those who consumed any hepatotoxic drug or alcohol more than 20 g/day, those with systemic illnesses such as diabetes mellitus, morbid obesity, congestive heart failure, and those with anti-HCV positivity were excluded.

Every subject underwent detailed history taking and clinical examination. Complete hemogram and liver biochemistry tests were done using an autoanalyzer (Synchron CX5 Clinical System, Beckman), and prothrombin time was measured using the Quick’s method manually. The cut-off
value for abnormal ALT was taken as 45 IU/L. Each subject’s serum was tested for HBsAg, HBeAg and anti HBe using commercially available microparticle enzyme immunoassay (MEIA) kits (Abbott Labs, Chicago). Anti HCV test was done using 3rd generation ELISA. Test for quantification of HBV DNA was done in sera of HBeAg-negative subjects (Amplicon HBV Monitor Assay, manual quantitative RT-PCR, Roche Molecular Systems, California) with lower limit of detection of 1000 copies/mL. A level of >10^5 copies/mL was considered as active/replicative infection. Liver biopsy was performed percutaneously using Tru-cut needle after obtaining informed consent. Adequate liver biopsy was defined when at least 1-cm-long piece was obtained, which had 3 or more portal triads. Histological activity index was assessed in each biopsy using modified Knodells score, in which a score <3 was considered minimal, 4-8 as mild, 9-12 as moderate, and 13-18 as severe chronic hepatitis.

Difference between the means was compared using the Student t-test and those between proportions using the chi-squared test. p value of <0.05 was considered significant.

Results

Nineteen subjects were detected during family screening of HBV-related chronic liver disease cases. In the remaining, 12 (40%) subjects had history of sexual promiscuity, ten had history of unsafe injection, and in 20, no clue was available for source of infection. The mean age in HBeAg-negative subjects (30.3 ± 9) y was higher than in HBeAg-positive subjects (18.9 ± 9) y; p<0.05). HBeAg-negative subjects formed the major group with 79% (48 of 61), and 41 of 48 were in the 21-40 years age group.

HBeAg-positive subjects had significantly higher ALT levels than HBeAg-negative ones. ALT was elevated in 32 (52%) subjects overall. HBV DNA quantification was done in HBeAg-negative subjects. Mean HBV DNA level was 2.19 x 10^5 (range 1.5 x 10^3 - 1.25 x 10^9) copies/mL. HBV DNA level was >10^5 copies/mL in 15 subjects (32%). The frequency of raised ALT in the DNA-positive and -negative subjects was 93% and 39%, respectively (p<0.05). Mean DNA level was significantly higher in subjects with raised ALT (3.57 ± 10^5 copies/mL) than in those with normal ALT (1.29 x 10^4 copies/mL; p<0.001).

Liver biopsy was done in 29 patients (12 HBeAg-positive, 6 HBeAg-negative chronic hepatitis B; 11 non-replicative infection). Fifteen (51.7%) showed chronic hepatitis (HAI >3). This was more commonly found in subjects with raised ALT (13 of 19) than those with normal ALT (2 of 10; p<0.05), but there was no difference in relation to HBeAg status. HAI>3 was noted in 4 of 6 cases who were DNA positive and in 7 of 12 of HBeAg-positive ones, and in 4 of 11 HBV DNA-negative subjects (p=0.05). All DNA-positive subjects with HAI >3 had raised ALT and with HAI <3 had normal ALT. Only one of four subjects with negative DNA and normal ALT had HAI>3. The median necro-inflammatory and fibrosis score was higher in DNA-positive subjects (HAI 7 vs. 3.5; fibrosis score 2 vs. 0).

Subjects were divided into three groups: Non-replicative (HBeAg negative, HBV DNA negative, normal ALT; n=33), HBeAg-negative chronic hepatitis (HBeAg negative, HBV DNA positive, normal or raised ALT; n=15), and HBeAg-positive chronic hepatitis (HBeAg positive, normal or raised ALT; n=13).

ALT values in patients in the replicative group were higher than those in the non-replicative group (Table). Similarly, replicative infection was more frequently associated with raised ALT (93% and 69%) than in the non-replicative group (27%), as well as more frequent HAI >3 (67% and 58%) than in the non-replicative group (36%).

Discussion

In our study, three-fourths of IDAHS subjects had evidence of seroconversion at the time of presentation. Studies from India and the West report HBeAg negativity in >80% of asymptomatic HBsAg carriers. The seroconverted subjects were a decade older than HBeAg-positive subjects, suggesting that seroconversion occurred in early adulthood in this group.
Asymptomatic chronic HBV infection

Transaminase elevation was noted in half of our subjects, and was related to DNA positivity as 93% of DNA-positive subjects had raised ALT and only 5% of subjects with normal ALT had raised DNA level. Similarly, HAI >3 was noted in half of the subjects and was related with raised ALT levels. ALT estimation in HBeAg-negative subjects can give a clue to replicative viral infection as only 5% of our HBeAg-negative cases with normal ALT had HBV DNA positivity. A similar finding has been noted in another study.11

Among DNA-positive subjects, HAI >3 was found in 4 of 6 subjects compared to only 4 of 11 DNA-negative subjects. An association between DNA positivity and histological activity has been observed in another Indian study.5 In the present study, median necro-inflammatory and fibrosis score was higher in DNA-positive subjects compared to DNA-negative subjects.

In summary, one-half of the IDAHS in our study had HBe seroconversion with HBV DNA-negative status, occurring beyond 20 years of age. A minority of these subjects had raised ALT (27%) or HAI >3 (36%), requiring periodical monitoring. The replicative infection noted in the other half was in the form of HBeAg positivity in 21% and HBV DNA positivity in 25% of the rest. The latter group was invariably associated with raised ALT and poor histology. HBV DNA testing in HBeAg-negative subjects with normal ALT appears to have little usefulness.

References


