

Original Article

Characterization of incidentally detected asymptomatic hepatitis B positive subjects in Egypt

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Abstract

Background: Although chronic hepatitis B virus infection is relatively common in Egypt, the incidental discovery of asymptomatic forms have not been well studied. **Aim:** To characterize the clinical, serological and histological liver damage among incidentally detected asymptomatic hepatitis B surface antigen (HBsAg)-positive subjects (IDAHS) in Egypt. **Methods:** We prospectively studied 70 consecutive IDAHS patients. Tests for liver function, serological markers for HBV, HCV, HDV and schistosomiasis were performed for all patients. HBV DNA was determined by the branched DNA technique and PCR. Liver biopsy specimens from 44 patients were studied and scored for activity and fibrosis stage by modified Knodell score and the METAVIR score. HBsAg and HBcAg were immunohistochemically evaluated in the liver tissue. **Results:** Of the studied 70 patients, 57 (81.6%) were HBeAg-negative and 13 (18.4%) were HBeAg-positive. Hepatic transaminases in HBeAg-positive patients were significantly elevated when compared to HBeAg-negative patients. HBV DNA was detected in only 3% of patients by the b-DNA technique and in 97% by PCR. Pathological examination of liver tissue revealed mild activity in 21 (47.7%) patients. Additionally, 21 patients (47.7%) revealed mild to moderate expansion of portal areas by fibrosis while 7 patients (15.9%) of them showed bridging fibrosis. None of the patients were cirrhotic. **Conclusion:** The majority of IDAHS subjects are HBeAg negative without elevation of hepatic transaminases. However, they should be considered as patients since viremia is detected in almost all cases using PCR technique, and histopathological evidence of chronic hepatitis B virus infection is present in varying degrees. **Key words:** Asymptomatic hepatitis B, histopathology, Modified Knodell, METAVIR.

Introduction

Hepatitis B virus (HBV) is one of the most common pathogens in the world. Annually up to 1 million die due to

the consequences of HBV infection such as cirrhosis and hepato-cellular carcinoma (1-3). About 12% of Egyptian patients with chronic liver disease were found positive for HBsAg (4) HBV genotype D is the most prevalent in Egypt (5). Incidentally detected asymptomatic hepatitis B surface antigen (HBsAg)-positive subjects (IDAHS) infected with genotype D were found to have a higher histological activity index (HAI) as compared to genotype A (6).

Chronic HBV carrier rate was found to be significantly higher among Schistosomal cases (12.5%) than non-Schistosomal individuals (6.2%) (7). The course and outcome of chronic hepatitis B virus infection is quite variable. Milder forms are non-progressive or only slowly progressive and are usually accompanied by the loss of serum HBV DNA and sero conversion from hepatitis B e antigen positive serology to e antibody positive serology (anti-HBe Ag).(8)

The prevalence of HBeAg-negative variant among HBV patients is quite variable through out the world, being high in Middle East countries; There are many reports that this mutant virus causes a more severe disease and is less responsive to treatment (9). El-Zayadi et al (10) reported that HBeAg – negative chronic hepatitis B represents more than 80% of chronic hepatitis B in Egypt.

This study is a trial to characterize HBV infection in incidentally detected asymptomatic hepatitis B surface antigen (HBsAg)-positive (IDAHS) among Egyptian subjects. The clinical, serological, biochemical and histological liver damage will be studied and correlated.

Patients and Methods

Patients

The study included 70 patients that presented at the outpatient clinic of the liver and Gastroenterology units of Mansoura, Tanta and Ain Shams University Hospitals from July 2001 to May 2002. All patients were incidentally detected

asymptomatic hepatitis B surface antigen (HBsAg) positive subjects (IDAHS) for at least 6 months. They were diagnosed during blood donation or during blood analysis before traveling abroad for work as having hepatitis B. All patients were subjected to thorough history taking stressing information about the possible routes of transmissions of HBV. Patients were excluded if they had one of the following: concomitant hepatitis C or any liver disease other than HBV, HDV, and schistosomiasis as well severe renal, hepatic, heart disease or malignancy.

Methods

1- Biochemical liver function tests including serum bilirubin, ALT, AST, prothrombin time and albumin, as well complete blood picture were done. Serological testing for HBV markers (HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgM and total anti-HBc), HCV and HDV markers (IgM and IgG) were determined by enzyme-linked immunosorbent assay (ELISA) (Abbot laboratory, Chicago, IL). Serological test for schistosomiasis was done by using the indirect hemagglutination assay (IHA) (11).

2- Testing for HBV DNA by the branched DNA technique and polymerase chain reaction (PCR) from pre-s/s and pre-c/c regions were done for all patients (12).

3- Abdominal ultrasound.

4- Percutaneous liver biopsy was performed for 44 patients using true cut liver biopsy (14 G, internal diameter 1.6 mm).

Pathology and Immunohistochemistry procedure for HBsAg and HBcAg

Pathological processing for liver biopsy specimens was as follows; 4 μ sections were prepared from paraffin blocks and stained for Hematoxylin & Eosin stain, Masson trichrom, Reticulin, PAS and PAS-diastase stains. Fibrosis and necroinflammatory changes were assessed and scored synchronously by modified Knodell score (Ishak score 13) and METAVIR score. (14 & 15) HBsAg and HBcAg immunohistochemistry were applied routinely to all liver biopsy specimens. Monoclonal antibodies to HBsAg and polyclonal antibody for HBcAg were applied (Zymed, South San Francisco, CA).

Statistical analysis

Statistical analysis was done by using SPSS statistical package for social science programs version 10, 1999. The data

were parametric by using Kolmogorov-Smirnov test. The qualitative data were presented in the form of number and percentage. Chi-square with Yate's correction was used. The quantitative data were presented in the form of mean, standard deviation and range. Student t test was used for comparison of two groups. Pearson correlation coefficient was used to study correlation between variables. Significance was considered when p less than 0.05.

Results

The 70 asymptomatic chronic HBV patients included in the study were 66 males and 4 females with mean age (31.47 \pm 7.81). Regarding the possible risk factors for HBV infection transmission, dentist consultation was recorded in 92.9%, schistosomiasis in 15.7%, and previous operation in 14.3% of patients. There was no history of drug abuse, blood transfusion or alcohol intake.

Biochemical and hematological results

Normal levels of hepatic transaminases were found in 97% of cases. Two patients had elevated liver enzymes who were also HBeAg-positive and one of them had antibodies against HDV. The liver function tests and hematological parameters are shown in Table 1.

Serological markers

All studied 70 patients were positive for HBsAg, all were positive for anti-HBcIgG and AntiHBe whereas anti-HBcIgM was negative in all patients. Thirteen patients (18.4%) were positive for HBeAg while 57 (81.6%) were negative for HBeAg. Anti-HBs was identified in 7.1% of patients, also, anti-HDV IgG was seen in only three patients (4.3%) (Fig.1). Only eleven patients (15.7%) were positive for schistosomiasis by the IHA test. The differences in liver function tests and haematological profile between HBeAg-positive and HBeAg-negative patients are shown in Table 2. There were significantly elevated ALT and AST levels in HBeAg-positive patients in comparison to the HBeAg-negative patients ($P < 0.001$).

Molecular biological techniques for detection of HBV DNA

The b-DNA technique detected HBV DNA in only 3% of patients who were also HBeAg-positive. On the other hand, the use of PCR for detection of HBV DNA by both the pre-s/s or the pre-c/c technique was highly sensitive and were identical to each other. Using PCR based assays, HBV DNA was detected in most patients (68) with anti-HBe (97.1%).

Pathology

Different pathological parameters are listed in Table 3. Mild and moderate capillarization of sinusoids was observed in 11 (27%) of the patients.

Regarding necroinflammatory injury, 21 (47.7%) of patients revealed mild activity, with score range (4-8), and 4 patients (10.1%) revealed moderate activity with score 9. On the other hand, 19 (43.2%) of biopsed patients revealed no or minimal activity by Ishak score. By METAVIR score 27 patients (61.4%) revealed different grades of activity.

Steatosis was identified in 11 out of the 44 biopsed patients (25%) with only one patient showing massive steatosis and most of them exhibit mild steatosis (Fig. 2).

Pertaining to fibrosis stage, 21 patients (47.7%) revealed mild to moderate expansion of portal areas while 7 patients (15.9%) of them showed bridging fibrosis. Sixteen (36%) of patients revealed no evidence of fibrosis and no patient was cirrhotic (Table 3).

In comparing HBeAg positive and HBeAg negative patients, no statistical difference was identified between the two groups when analyzing the necroinflammatory injury or fibrosis stage, both by applying Ishak and METAVIR scoring systems (Table 4). There was 100% concordance between the two scoring systems regarding the fibrosis stage, however, there was no such concordance in evaluation of necroinflammatory activity. By METAVIR, there is higher estimation of degree of necroinflammation.

Ground glass hepatocytes were mostly observed in clusters, in between uninvolved hepatocytes, without acinar zone distribution. Less commonly ground glass hepatocytes were seen singly scattered. Clustering of hepatocytes was associated with lack of significant necroinflammatory injury. The percent of involved hepatocytes ranged from <5% - >75% of hepatocytes.

Considering the correlation between pathological parameters and laboratory findings, the significant correlations were between ALT, and modified HAI, fibrosis stage by Ishak and with fibrosis stage by METAVIR (Table 5). Moreover, there was a significant correlation between ALT and each of the individual parameters of necroinflammation in liver biopsy: PMN, portal inflammation, and focal parenchymal necrosis. Platelet number was inversely correlated with HAI, and fibrosis stage, however, this was lacking statistical significance.

Immunohistochemical staining for HBsAg & HBeAg

HBeAg was positive in 12 (27.2%) of biopsed cases. The HBeAg was mainly found to be cytoplasmic with less evident nuclear reaction (<10% of hepatocytes). However, predominant nuclear reaction was identified in 5 cases. The latter pattern was associated with necroinflammatory activity. Eight (21.1%) of the 38 HBeAg-negative patients revealed positive tissue HBeAg by immunohistochemistry. Only four out of the six patients HBeAg-positive were positive for HBeAg in liver biopsy, while the other two patients (33.3%) were negative (Table 4). HBsAg, was positive in all 44 cases, cytoplasmic mostly in clusters of hepatocytes, and less commonly singly scattered (Fig. 2). Membranous staining HBsAg was uncommon and was seen either alone or in conjunction with the cytoplasmic pattern associated with nuclear HBeAg reaction (Fig. 3).

Only two patients out of the biopsed 44 individuals demonstrated bilharzial granuloma in the liver tissue. The 42 other biopsy specimens revealed no pathologic evidence of bilharzial affection.

Discussion

This current study showed that 81.6% of our patients were HBeAg negative which is very similar to El-Zayadi et al (10) who found that more than 80% of chronic hepatitis B cases were HBeAg negative. This high occurrence of HBeAg negative chronic HBV infection is comparable to other studies reported in Middle East and Mediterranean countries (5, 15, 16, 17). However, this is different from the results reported from France (22%) (18) and the US (54%) (19). The frequency of HBeAg-positivity in our study was 18.4%, which is comparable to the data reported in sub-Saharan Africa (20.5%) (20) and Iran (12%) (16) but lower than the 40% prevalence reported in the far east (21). The geographic variation of HBeAg negative chronic hepatitis B has a direct relation to the genotype distribution. Saady et al (5) had reported that HBeAg disappears early in patients with HBV genotype D, which is the predominant genotype in Egypt, because of early stop codon mutation. The high prevalence of dentistry contact (93%) in our patients may direct our attention for further studies aiming at disclosure of the possible role of dentistry clinics in HBV transmission. The low figure of schistosomal positivity, 15.7%, may reflect the lack of significant epidemiological association or possibility of being risk factor. This is in contrast to Madwar et al (22) who found that minotransferas contributes significantly in increased HBV infection. In our study, hepatic transaminases levels were found to be normal in 97% of the asymptomatic chronic HBV patients.

In the current study, only 3% of our patients were +ve HBV DNA in serum using b-DNA technique, however, using PCR pre-s/s or pre-c/c DNA was +ve in 97% which proves the higher sensitivity of detection by the latter technique. This in agreement with Lindh et al, (23) and Kessler et al, (24) who found that using PCR assays, the majority of patients with chronic HBV infection, including those who are hepatitis B e antibody positive have detectable HBV DNA. We found coincidence of HBsAg and anti-HBs in 7% of patients. The protective anti-HBs antibody is directed against the (a) determinant of HBsAg. In most instances of coincident HBsAg and anti-HBs, the antibodies are directed against one of the determinants other than the (a) determinant and are unable to neutralize the circulating virions (25). Coexistence of HBsAg and anti-HBs has been reported in 24% of HBsAg-positive individuals in Iran (26). In the present study 4.2% of asymptomatic chronic HBV infections have coexistent hepatitis delta virus antibodies. Positive anti-HD was reported in 8.3%(27) and in 10.5% (5) of otherwise healthy Egyptians positive for HbsAg.

Presence of early stages of fibrosis in 21 (47.7%) of the biopsed 44 IDAHS patients and even, presence of bridging fibrosis in 7 (15.9%) of them may reflect the importance of liver biopsy in assessment of such patients irrespective of serology or enzyme profile. Absence of cirrhosis in any of all biopsed 44 IDAHS patients, and even complete absence of fibrosis in 36% of the patients may reflect the relative favorable behavior of such individuals. In addition, presence of significant necroinflammatory (HAI 4-9) in >50% of biopsed patients is in contrast to Martinot-Peignoux et al (28) and Ben Rejeb et al (29) who reported minimal activity in such hepatitis B patients with normal enzymes. However in agreement with Thakur et al (6) who found that genotype D is associated with more severe liver disease. Presence of significant correlation between ALT, HAI and fibrosis may help in follow up of those patients. This is in agreement with Yalcin et al (30) who reported that monitoring of ALT is of value in assessing hepatocellular damage in patients with chronic hepatitis B virus infection. They also, suggested that HBeAg-negative patients with elevated ALT levels and some with normal ALT levels should be considered highly infectious in the course of chronic HBV infection. Lack of significant difference between HBeAg positive and HBeAg negative patients groups in regard to the necroinflammatory injury or fibrosis stage is in agreement with Yalcin et al (30). In the present work, 21.1% of patients with negative serum HBeAg, demonstrated HBcAg in liver tissue by immunohistochemistry. On the

other hand 33.3% of patients with positive serum HBeAg were found to be negative for HBcAg in liver tissue by immunohistochemistry. This may indicate that serum HBeAg status does not reflect the active replication of hepatitis B virus in liver tissue, and routine staining for HBsAg and HBcAg in chronic hepatitis B patients is valuable in reflecting hepatitis B pathology. In agreement with Chu and Liaw (31) membranous staining of HBsAg on the hepatocyte was seen associated with nuclear HBcAg reaction and thus can be recognized as a sensitive and specific marker of active hepatitis B virus replication. Predominant nuclear reaction of HBcAg pattern was associating necroinflammatory activity that reflect viral replication as it was reported by Chu et al (32) This is in contrary with Sharma et al (33) who found no significant correlation between the pattern of HBsAg or HBcAg expression and HAI score. The mechanism of intrahepatic shift of HBcAg from the nucleus to the cytoplasm and the decreased levels of minotra in this phase may be, at least in part, secondary to liver damage and regeneration.(34)

We found steatosis in our patients was found in 11 patients (25%). The steatosis was mostly mild, comparable to that of Czaja et al (35) who identified fat deposition in 22% of chronic hepatitis B, however, lower than findings reported by Malhotra et al (36) who found steatosis in 66.6% of chronic hepatitis B patients in comparison to 70% of HCV patients. Shah et al (37) found no steatosis in any of studied 34 chronic hepatitis B patients.

Conclusions

We conclude that IDAHS subjects had positive HBV DNA with varying histopathological activity and fibrosis. Those subjects practically considered as patients, with predominance of HBeAg-negative pattern.

For complete diagnosis and proper selection for treatment; PCR for HBV DNA, together with routine immunohistochemical staining for HBsAg and HBcAg should be done and interpreted in the light of biochemical and serological results.

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Table 1. Liver function tests and hematological parameters of the studied 70 patients.

Parameters	Mean \pm SD
Albumin level (gm%)	4.39 \pm 0.29
Bilirubin level (mg%)	0.816 \pm 0.18
ALT level U/L	32.06 \pm 20.94
AST level U/L	28.51 \pm 12.5
Hemoglobin level (gm%)	12.97 \pm 1.07
WBCs count x 10 ³	6.177 \pm 1.10
Platelet count x 10 ⁶	209.63 \pm 52.98

ALT, alanine _minotransferases. AST, aspartate _minotransferases. WBCs, white blood cells.

Table 2. Liver function tests and haematological profile between HbeAg-positive and HbeAg-negative patients

Parameters	HbeAg-ve (n=57)	HbeAg+ve (n=13)	P
ALT	27.42 \pm 4.72	52.38 \pm 23.21	0.001
AST	25.43 \pm 4.5	39.85 \pm 15.16	0.001
Albumin	4.34 \pm 0.285	4.36 \pm 0.032	0.71
Bilirubin	0.805 \pm 1.189	0.862 \pm 0.126	0.31
WBCs	6.29 \pm 1.149	5.671 \pm 0.72	0.23
Platelets	208.7 \pm 52.12	213.64 \pm 58.69	0.76
Hemoglobin	13.02 \pm 1.06	12.75 \pm 1.13	0.411

ALT, alanine _minotransferases. AST, aspartate _minotransferases. WBCs, white blood cells.

Table 3. Pathological parameters of the biopsed 44 patients

Parameters	Number	Mean \pm SD	Range
Modified HAI	44	4.18 \pm 2.81	0-9
Fibrosis	44	1.34 \pm 1.33	0-5
Steatosis	11/44	0.36 \pm 0.72	0-3
Capillarization	12/44	0.41 \pm 0.76	0-3

HAI, histological activity index.

* HAI score: (0-18) ** Fibrosis score: (0 – 6)

Table 4. Comparison between HBeAg positive and HBeAg negative patients regarding the necroinflammatory injury and fibrosis, both by applying Ishak and METAVIR scoring systems, as well HBeAg immunohistochemistry (IHC).

Parameters	Total (n=44)	HBeAg-ve (n=38)	HBeAg+ve (n=6)	p-value
Ishak score: Modified HAI (0-18)				
0-3	19 (43.2%)	17 (44.7%)	2 (33.3)	0.520
4-8	21 (47.7%)	17 (44.7%)	4 (66.7%)	
9	4 (10.1%)	4 (10.6%)	0 (0%)	
Fibrosis score (0-6)				
0	16 (36.4%)	13 (34.2)	3 (50%)	0.719
1-2	21 (47.7%)	19 (50%)	2 (33.3%)	
3-5	7 (15.9%)	6 (15.8%)	1 (16.7%)	
METAVIR score Activity (A0-3)				
A0	17 (38.6%)	14 (36.8)	3 (50%)	0.229
A1	18 (41%)	17 (44.7)	1 (16.7%)	
A2	6 (13.6%)	4 (10.6%)	2 (33.3%)	
A3	3 (6.8%)	3 (8%)	0 (0%)	
Fibrosis (F0-4)				
F0	16 (36.4%)	13 (34.2)	3 (50%)	0.766
F1	21 (47.7%)	19 (50%)	2 (33.3%)	
E2	5 (11.4%)	4 (10.6%)	1 (16.7%)	
F3	2 (4.5%)	2 (5.2%)	0 (0%)	
Tissue HBeAg IHC				
Positive	12 (27.2%)	8 (21.1%)	4 (66.7%)	
Negative	32(72.8%)	30 (78.9%)	2 (33.3%)	

Table 5. Correlation between Laboratory Finding and Pathology of biopsed 44 cases

Histo pathology Parameters	ALT		AST		S.Albumin		Platelets		HGB.	
	R	p	r	p	r	p	r	p	r	p
HAI	0.53	<0.001	0.116	0.45	0.008	0.96	0.277	0.076	0.115	0.45
Fibrosis	0.46	<0.001	0.145	0.38	0.13	0.37	0.247	0.106	0.025	0.87
PMN	0.389	0.009	0.078	0.615	0.12	0.43	0.26	0.088	0.97	0.53
Portal Inflam.	0.402	0.007	0.045	0.77	0.043	0.78	0.27	0.072	0.015	0.30
Focal necrosis	0.378	0.011	0.07	0.65	0.108	0.485	0.121	0.43	0.013	0.93
Confluent nec.	0.16	0.278	0.06	0.66	0.032	0.83	0.098	0.52	0.013	0.93
Steatosis	0.025	0.87	0.13	0.38	0.14	0.35	0.098	0.52	0.093	0.54
Capillarization	0.369	0.014	0.06	0.69	0.15	0.322	0.097	0.53	0.150	0.33
METAVIR										
A	0.29	0.652	0.12	0.43	0.062	0.69	0.098	0.52	0.028	0.85
F	0.358	0.017	0.104	0.503	0.16	0.29	0.208	0.173	0.088	0.57

Figure 1. Positive serological markers for the studied group.

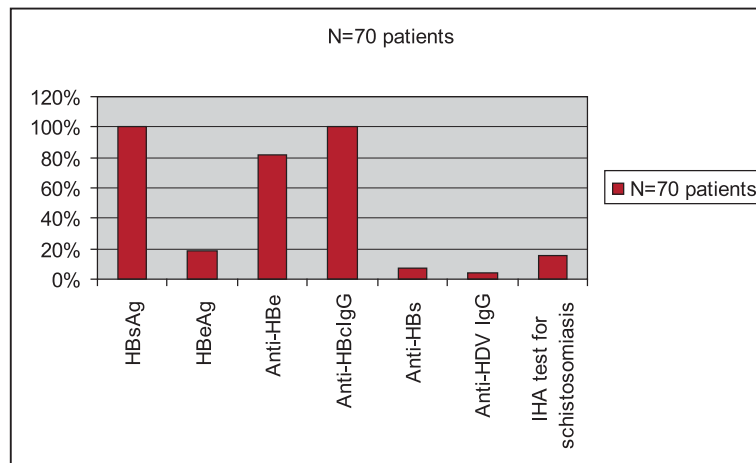


Figure 2. Hepatitis B; Positive membranous HBsAg, reaction is strictly membranous (Peroxidase x400).

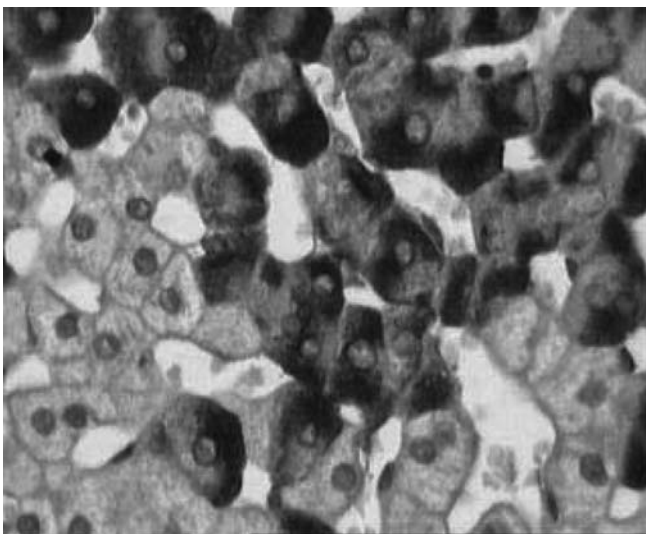


Figure 3. Hepatitis B; Positive membranous HBsAg, cytoplasmic reaction with adjacent negative hepatocytes (Peroxidase x400).

