Annals of Gastroenterology (2014) **27,** 60-64

Bilirubin, aspartate aminotransferase and platelet count score: a novel score for differentiating patients with chronic hepatitis B with acute flare from acute hepatitis B

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Abstract

Background Early therapy improves the outcome in patients with chronic hepatitis B with acute flare (CHB-AF). However in mesoendemic countries, it is difficult to differentiate CHB-AF from acute hepatitis B (AHB). The aim of this study was to formulate a clinical score to differentiate CHB-AF from AHB in patients presenting with an acute hepatitis-like picture.

Methods Patients with a protracted clinical course of >2 months with elevated liver enzymes and positive hepatitis B virus DNA, who had undergone liver biopsy were included in this study. The clinical and laboratory profiles were compared between patients with biopsy suggestive of CHB-AF and AHB.

Results Of the 75 patients included, 32 patients had a liver biopsy suggestive of CHB-AF. At 6 months, HBsAg clearance was lower in the CHB-AF group (9.4 vs. 76.7%). Presence of prodrome, platelet count, aspartate aminotransferase (AST), alanine aminotransferase and bilirubin levels and presence of anti-core antibody (IgM anti HBc) were lower in CHB-AF group (P<0.01). Using the receiver operating characteristic curve, peak bilirubin level, peak AST levels and least platelet count within the first 8 weeks had the highest predictive power. Optimal values of platelet <2.4x10^5/μL, peak bilirubin <4.5 mg/dL and AST <550 IU/L were given a point each. On internal validation a score of 2 had 86% specificity, 70.1% sensitivity and 82.7% diagnostic accuracy in predicting CHB-AF.

Conclusion Bilirubin, AST and platelet count (BAP) score may be helpful in differentiating CHB-AF from AHB. A score of >2 could strongly suggest CHB-AF. However the score requires further validation.

Keywords BAP score, chronic hepatitis B with acute flare (CHB-AF), acute hepatitis B (AHB)

Ann Gastroenterol 2014; 27 (1): 60-64

Introduction

Hepatitis B infection is a major health problem in India. India is mesoendemic for chronic hepatitis B (CHB) infection. The prevalence of hepatitis B virus (HBV) infection is estimated to be 2-8% [1]. There is 4% lifetime risk of developing HBV infection among newborns in India [2]. When patients with HBV infection present with acute hepatitis, it may be a true acute hepatitis B (AHB) or an acute flare of chronic hepatitis B (CHB-AF) not yet diagnosed. It is important to distinguish patients with AHB, mostly self-limited, from those with CHB-AF who will benefit from treatment with antiviral agents [3]. However the high prevalence of HBV infection in India makes it difficult to distinguish between these two conditions. Liver biopsy is the gold standard investigation to differentiate between them. However there are no studies to date based on liver biopsy differentiating CHB-AF from AHB. We performed this study to identify the clinical, biochemical and virological parameters to differentiate between acute hepatitis B (AHB) and acute flare in chronic hepatitis B (CHB-AF) in patients presenting with a prolonged acute hepatitis-like picture and to formulate a score to identify patients with CHB-AF.

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Conflict of Interest: None

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Received 13 March 2013; accepted 30 June 2013

Materials and methods

A retrospective study was done in a tertiary care centre in south India between January 2008 and December 2011. All hepatitis B surface antigen (HBsAg)-positive patients who had presented with a protracted acute hepatitis-like picture with a persistent elevation of alanine aminotransferase (ALT) >5 times upper limit of normal for more than 8 weeks were included in the study. All these patients should have undergone a liver biopsy. Patients with prior diagnosis of chronic HBV infection or cirrhosis were excluded. Those with history of significant alcohol intake (defined as >40 g/day for males and >20 g/day for females), another documented hepatotropic or non-hepatotropic infection or documented intake of hepatotoxic medications within 6 months prior to presentation were excluded. Further patients whose liver biopsy revealed an alternative diagnosis were also excluded from the study.

Data was collected from the medical records of all patients fulfilling the inclusion and exclusion criteria. Data regarding age, gender, presence of prodrome, liver consistency (as felt by the examiner on palpation and classified as soft, firm or hard), presence of splenomegaly, laboratory parameters like hemoglobin, platelet count, bilirubin, ALT, aspartate aminotransferase (AST) and albumin levels and virological parameters like anti -ore antibody (IgM anti HBc) using the Architect Chemiluminescent Microparticle Immunoassay (CMIA), hepatitis B e antigen (HBeAg) and HBV DNA levels were collected. Prodrome was defined as the presence of fever, fatigue malaise or joint pains prior to onset of jaundice. The patients included in the study had their liver function tests and platelet levels done, weekly in the first month, and once in two weeks during the second month. We selected the highest and the lowest levels from these results. Virological parameters were done at the time of initial presentation. Liver biopsy was done between the 8th and 10th week of onset of illness in all newly diagnosed HBsAg-positive patients who had persistent elevation of ALT as per the institutional protocol that was followed during the study period. Liver biopsy reports were collected from the medical records. Lobular disarray, ballooning degeneration, apoptotic bodies and lymphocyte-predominant lobular and portal inflammation to a variable extent, was present in all cases. In the presence of more than stage 2/6 fibrosis (Ishak stage) and the presence of ground glass hepatocytes or Shikata's orcein-positive cells, the patient was diagnosed as having CHB-AF. Shikata's orcein stain is a specific, relatively inexpensive, easily performed method to stain hepatitis surface antigen [4]. The 27 biopsies available were verified by another pathologist and the findings were consistent. In 23 (85%) biopsies there was agreement in the findings. In 4 patients with CHB-AF there was disagreement regarding the stage of fibrosis. However since the stage of fibrosis did not alter the final diagnosis of CHB with flare, the findings were considered consistent. Based on the biopsy reports, the patients were divided into 2 groups, those with AHB and those with CHB-AF. HBsAg status at 6 months after the onset of the disease was assessed by phone interview with the patients.

The collected data among the groups with AHB and CHB-AF in liver biopsy was analyzed statistically using SPSS version 20.0 and P value <0.05 was considered statistically significant. Quantitative parameters were analysed using the Student's *t* test and qualitative parameters using the chi square test. Between parameters with a statistically significant difference in the 2 groups, receiver operating characteristic (ROC) curves were plotted, and optimum values identified among the parameters with maximum area under ROC curve. A score was formulated and internal validation was performed.

Results

Of the total 109 patients included in the study 34 patients were excluded. 23 patients had history of significant alcohol intake, 7 patients had histological evidence of drug induced liver injury, 3 patients had hepatitis C virus infection and one patient had serological evidence of cytomegalovirus infection. Of the remaining 75 patients, 32 had CHB-AF and 43 patients had AHB on the basis of liver biopsy results. There was no statistically significant difference in age (40 vs. 40.4 yrs) or gender between CHB-AF and AHB groups (P>0.1). 28.1% patients in the acute flare (CHB-AF) group compared to 55.8% of the AHB patients reported a prodrome (P=0.017). There was no statistically significant difference in liver consistency and presence of splenomegaly between the 2 groups (P>0.05) (Table 1). Among the laboratory parameters, least platelet count, peak bilirubin, peak ALT and peak AST levels (within

Table 1 Distribution of baseline parameters among patients with CHB-AF and AHB

	CHB-AF	AHB	P value
Mean age (years)	40 ± 11.1	40.4 ±16.4	0.894
Proportion of males	96.9 %	92.4 %	0.082
Prodrome	28.1 %	55.8 %	0.017
Firm liver consistency	28.1 %	41.9 %	0.112
Splenomegaly	18.8 %	37.2 %	0.343

CHB-AF, chronic hepatitis B with acute flare; AHB, acute hepatitis B

Table 2 Distribution of laboratory parameters among patients with CHB-AF and AHB

Parameter	CHB-AF		AHB		P value
	Mean	Std dev	Mean	Std dev	
Platelet (/μL)	2.01 (10^5)	0.62	2.83 (10^5)	0.89	<0.001
Bilirubin (mg/dL)	5.4	2.4	13.3	3.06	<0.001
ALT (IU/L)	609.4	146.8	1460	212.6	0.003
AST (IU/L)	405	104.9	1022.9	115.9	<0.001
Albumin (g/dL)	3.95	0.1	3.7	0.09	0.057

CHB-AF, chronic hepatitis B with acute flare; AHB, acute hepatitis B; ALT, alanine aminotrasnferase; AST, aspartate aminotransferase

the first 8 weeks) were significantly different among the two groups (Table 2). However there was no significant difference among the albumin levels. Among the virological parameters, only presence of IgM Anti HBc was significantly different with 86% in the AHB group and only 40.6% in the CHB-AF group showing positivity (P=0.001) (Fig. 1). There was no statistically significant difference in HBV DNA levels and positivity of HBeAg between the two groups. At 6 months after the initial presentation, HBsAg was negative in 9.4% of patients in the CHB-AF group compared to 76.7% in AHB group (P<0.05).

ROC curves were plotted were all parameters which showed significant difference among the 2 groups. Least platelet count, peak bilirubin, and peak AST levels (within the first 8 weeks) had maximum area under ROC curve (AUROC) (Fig. 2). To identify patients with CHB-AF optimum cut-off values were identified as peak bilirubin level <4.5 mg/dL, peak AST level <550 IU/L and least platelet count <2.4 x 10^5 /μL. Each of these values was given a score of 1 each and the cumulative bilirubin, AST and platelet count (BAP) score was calculated. On internal validation, a BAP score of 2 had the maximum diagnostic accuracy (82.7), with a sensitivity of 78.1%, specificity of 86%, positive predictive value of 80.6% and a negative predictive value of 84.1% (Table 3).

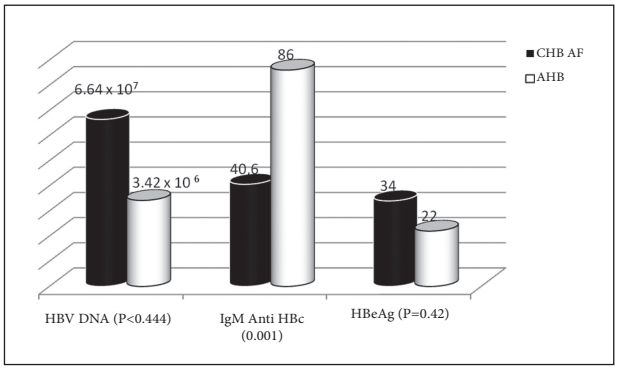

Figure 1 Distribution of virological parameters among patients with CHB-AF and AHB

CHB-AF, chronic hepatitis B with acute flare; AHB, acute hepatitis B; HBV DNA, hepatitis B virus DNA; IgM Anti HBc, anti core antibody; HBeAg, hepatitis B e antigen

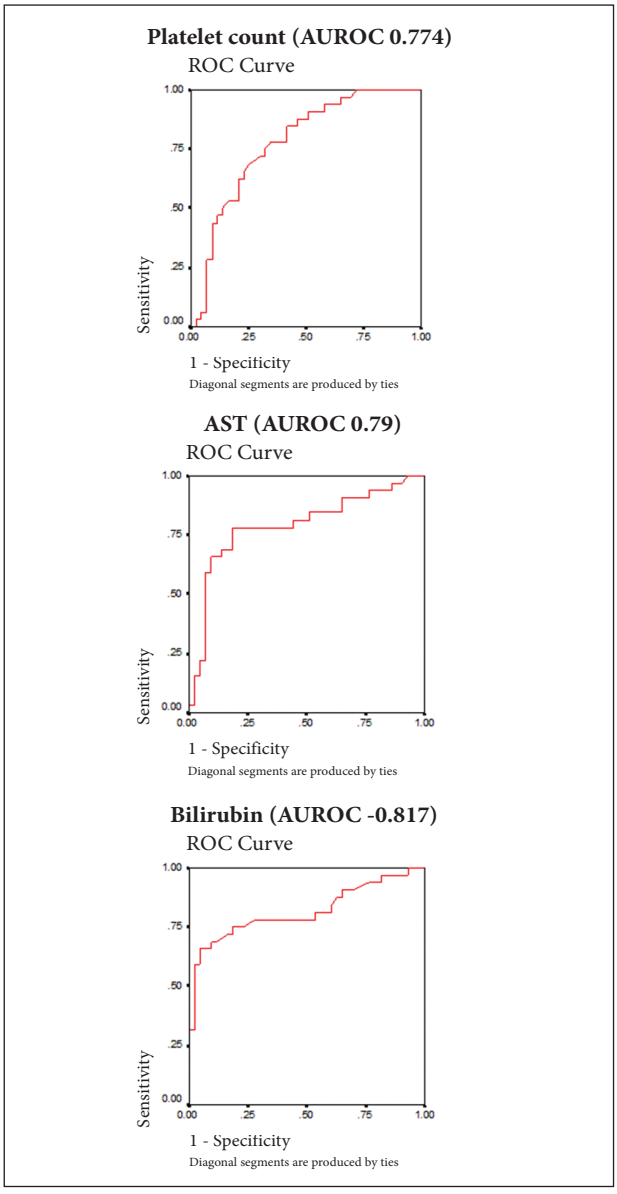

Figure 2 Receiver operating characteristic (ROC) curves

AUROC, area under receiver operating characteristic; AST; aspartate aminotransferase

Table 3 Results of internal validation of nilirubin, aspartate aminotransferase and platelet count (BAP) score

Score	1	2	3
Sensitivity	96.9	78.1	46.9
Specificity	48.8	86.0	100.0
False negative	3.1	21.9	53.1
False positive	51.2	14.0	0.0
Predictive value of positive test	58.5	80.6	100.0
Predictive value of negative test	95.5	84.1	71.7
Accuracy	69.3	82.7	77.3

Discussion

HBV infection leads to considerable mortality and morbidity in India with a prevalence of 2-8% reported in most studies. It is estimated that there are around 50 million HBV carriers in India, thus forming the second largest global pool of chronic HBV infection [1]. Vertical transmission from mother to child is a common mode of transmission in India with a 4% life-time risk of acquiring HBV infection among newborns [2]. However HBV infection remains asymptomatic in most individuals, >95% of patients with AHB infection recover spontaneously and do not require any treatment. However an acute hepatitis-like picture in patients with HBV infection may be true AHB (AHB) or CHB-AF. In countries with high or intermediate endemicity for HBV infection the distinction between true severe AHB and reactivation of CHB may be difficult. It is important to distinguish patients with AHB, mostly self-limited, from those with CHB-AF who will benefit from treatment with antiviral agents [3]. To differentiate between these conditions a liver biopsy may be required [5]. However, there are very few studies in published literature attempting to differentiate between these two scenarios. Further, available studies [6,7] use HBsAg clearance rather than liver histopathology to arrive at a diagnosis.

In our study the two groups were age- and sex-matched. Prodromal symptoms like fever, myalgia and nausea were significantly lower in the group with CHB-AF. Similar results were seen in the study conducted by Han *et al* [6] where patients in the acute hepatitis group were more symptomatic. Han *et al* [6] found that splenomegaly was commoner in the AHB group. However, no such difference was seen in our study where the least platelet count, the peak bilirubin level and the peak ALT and AST levels (all measured within the first 8 weeks) were significantly different among the two groups. Han *et al* [6] and Kumar *et al* [7] did not find any significant difference between the hematological or laboratory parameters among the two groups. However, in both these studies the initial levels at presentation were considered, while our study considered the peak value and the least value within the first 8 weeks of presentation. These results were in accordance with the higher intensity of necroinflammatory activity noted in biopsy specimens in the patients with AHB compared to those with CHB-AF.

Among the virological parameters, presence of IgM Anti HBc was significantly different with 86% in the AHB group and only 40.6% in the CHB-AF group showing positivity. This was similar to the results of other published studies [6-8]. This could be because of the fact that hepatocellular injury in AHB is mostly immunological resulting in clearance of virus while in CHB-AF it is associated with increased viral replication [9]. Unlike other studies, there was no statistically significant difference in HBV DNA levels between the two groups. This could be because of the fact that DNA levels were analyzed using different analyzers. At 6 months after the initial presentation, HBsAg was negative in 76.7% of patients in the AHB group, which is much lower than expected (>95%) [10]. This may be due to the fact that only patients with protracted acute hepatitis were included in this study. 9.4% of patients in the CHB-AF group cleared HBsAg within 6 months.

Our study has limitations as our score has to be validated in an external cohort. Furthermore, whether the results would be applicable in a population with low endemicity needs to be studied. We included only those patients with a protracted AHB-like picture lasting more than 8 weeks. This was because liver biopsy was mostly done once the acute phase had stabilized and the diagnostic confusion persisted. Patients with fulminant acute hepatitis or hepatitis which resolved within 8 weeks were excluded as there was no treatment dilemma in those groups. Hence this score could be used to avoid the delay of 6 months for the initiation of antiviral therapy in patients with CHB-AF. The follow-up period is only 6 months in our study. Lastly, in our study all the patients were from south India. Hence, further studies will be needed to assess the applicability of the score in the western population. Currently, we have undertaken a 3-year prospective study to validate this score in HBsAg-positive patients presenting with acute hepatitis-like picture with HBsAg clearance at 1 year as the primary outcome.

In conclusion, presence of prodrome, platelet count, bilirubin level, liver enzyme levels and presence of IgM anti-HBc were statistically different between patients with AHB and CHB-AF. BAP score is helpful in differentiating CHB-AF from AHB. A score of >2 could strongly suggest a diagnosis of CHB with flare. This could avoid unnecessary delay in the initiation of antiviral therapy. However, further studies including larger numbers of patients are warranted to validate this score.

Summary Box

What is already known:

- Hepatitis B-related acute hepatitis may be a true acute hepatitis B (AHB) or an acute flare of chronic hepatitis B (CHB-AF) not yet diagnosed
- It is important to identify CHB-AF as early therapy will be beneficial
- In mesoendemic countries it is difficult to distinguish between these two conditions
- IgM anti-core antibody, hepatitis B DNA and HBeAg levels have been shown to be significantly different between the 2 groups in some early studies
- Liver biopsy is the gold standard investigation to differentiate between them, however, there are no studies to date based on liver biopsy differentiating CHB-AF from AHB

What the new findings are:

- Presence of prodrome, platelet count, bilirubin levels, liver enzyme levels and presence of IgM anti HBc were statistically different between patients with AHB and CHB-A
- Bilirubin, aspartate aminotransferase and platelet count (BAP) score is helpful in differentiating CHB-AF from AHB
- A BAP score of 2 could strongly suggest a diagnosis of chronic hepatitis B with flair
- This is the first liver biopsy-based study to differentiate acute flare from true acute hepatitis

References

1. Datta S. An overview of molecular epidemiology of hepatitis B virus (HBV) in India. *Virol J* 2008;**5**:156.
2. Acharya SK, Madan K, Dattagupta S, Panda SK. Viral hepatitis in India. *Natl Med J India* 2006;**19**:203-217.
3. Lok ASF, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007;**45**:507-539.
4. Henwood A. Current applications of orcein in histochemistry. A brief review with some new observations concerning influence of dye batch variation and aging of dye solutions on staining. *Biotech Histochem* 2003;**78**:303-308.
5. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012;**57**:167-185.
6. Han Y, Tang Q, Zhu W, et al. Clinical, biochemical, immunological and virological profiles of, and differential diagnosis between, patients with acute hepatitis B and chronic hepatitis B with acute flare. *J Gastroenterol Hepatol* 2008;**23**:1728-1733.
7. Kumar M, Jain S, Sharma BC, Sarin SK. Differentiating acute hepatitis B from the first episode of symptomatic exacerbation of chronic hepatitis B. *Dig Dis Sci* 2006;**51**:594-599.
8. Rodella A, Galli C, Terlenghi L, Perandin F, Bonfanti C, Manca N. Quantitative analysis of HBsAg, IgM anti-HBc and anti-HBc avidity in acute and chronic hepatitis B. *J Clin Virol* 2006;**37**:206-212.
9. Chang KM. Hepatitis B immunology for clinicians. *Clin Liver Dis* 2010;14:409-424.
10. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009;**50**:661-662.