Acute Episodes of Hepatitis in Chronic HBV Infection "Etiological Considerations in Turkey"

TÜRKİYE'DE KRONİK HEPATİT B VİRÜS İNFEKSİYONLARINDA AKUT ALEVLENMELERİN ETYOLOJİK YÖNDEN DEĞERLENDİRİLMESİ

Fatih BEŞIŞIK, MD., Prof.Süleyman YALÇIN, M.D., Prof.Atilla ÖKTEN, M.D., Levent ERDEM, M.D., Sabahattin KAYMAKOĞLU, M.D., Güngör BOZTAŞ, M.D., Yılmaz ÇAKALOĞLU, M.D.

* Professor of Gastroenterohepatology
** Associate Professor of Gastroenterohepatology
istanbul Medical Faculty, Department of Gastroenterohepatology, İSTANBUL

SUMMARY

Forty Turkish patients (30 males, 10 females, mean age: 38.5±15.4 years) with chronic hepatitis B virus (HBV) infection and acute episodes of hepatitis were studied to determine the releavent etiologies of these exacerbations. Forty percent of the acute attacks were the result of superinfection with other non-B viruses, more than an half of which were due to HDV superinfection, whereas roughly two-thirds were due to changes in HBV activity state (spontaneous inactivation and reactivation of HBV replication). There was no discernible difference between HBeAg positive (n=15) and anti-HBe positive (n=25) patients in regard to superinfection with other non-B viruses, clinical and biochemical features.

Key Words: Chronic hepatitis B virus (HBV) infection, Acute exacerbations, Acute episodes of hepatitis

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ÖZET

Kronik hepatit B virusu (HBV) infeksiyonlu ve akut hepatit atağı geçirmekte olan 40 Türk hastada (30 erkek, 10 kadın, ortalama yaş: 38.5+15.4 yıl) bu alevlenmelerin sebebleri araştırıldı. Hastaların %40'ında, yarısından çoğunda delta virusu olmak üzere, diğer bir non-B virusu ile süperinfeksiyon söz konusu idi. Vakaların yaklaşık 2/3'ünde ise HBV'nun aktivasyon düzeyindeki değişmeler (HBV replikasyonunun spontan inaktivasyonu veya reaktivasyonu) akut alevlenmeden sorumlu bulundu. Diğer non-B virusları ile süperinfeksiyon açısından karşılaştırıldığında, HBeAg-pozitif (n=15) ve anti-HBe pozitif (n=25) hastalar arasında anlamlı bir farklılık tespit edilmedi.

Anahtar Kelimeler: Kronik hepatit B virusu (HBV) infeksiyonu, Akut alevlenme, Akut hepatit atağı

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Chronic HBV infection is a widespread and serious health problem in Turkey with a 4-10% HBsAg seropositivity rate (1). This means 2.5-6 million chronically HBV infected people with a disease spectrum ranging from asymptomatic HBsAg carrier state to decompansated liver cirrhosis and hepatocelluler carcinoma (HCC), which necessitates to study the relevant etiologies and clinicopathological features of the acute episodes of hepatitis in this population.

MATERIALS AND METHODS

Patients: Forty (30 males, 10 females, mean age: 38.5±15.4 years) patients who were admitted to our department in 1991 and 1992 and fulfilled all of the following criteria included in this study: a) Chronic HBV infection (Serum HBsAg remained positive for at least 6 months on follow-up) b) Presenting symptoms and signs compatible with acute hepatitis c) Abrupt increase in serum levels of aminotransferases to at least 5 times of the previous value d) Decrease in serum levels of transaminases toward to the normal after acute episode. Drugs and alcohol were excluded as likely etiological agents. Intravenous drug abusers, homosexuals or polytransfused subjects, patients under INF or any other immunological and antiviral treatment were excluded. Diagnostic classification was mode according to the accepted criteria (2,3): HBsAg carrier state (13 patients), chronic persistent hepatitis (7 patients), chronic active hepatitis (16 patients), liver cirrhosis (4 patients). All of the patients had been tested for HBsAg, Anti-HBc, HBeAg, anti-HBe, HBV DNA, anti-delta, anti-HCV, anti-HSV, anti-CMV, anti-EBV, serum biochemistry (albumin, globulin, bilirubin, alkaline

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Correspondence: Fatih BEŞIŞIK M.D.
Istanbul Medical Faculty
Department of Gastroenterohepatology
İSTANBUL

phosphatase, gamma glutamyl transpeptidase, aspartate aminotransferase (AST), alanine aminotransferase (ALT) on initial admission. Routine follow-up studies included clinical evaluation, liver biochemical tests, serological markers for hepatitis virus infection and assays for alpha-fetoprotein. Additional tests for detection of anti-HAV IgM, anti-HBe IgM, HBV DNA titer, delta antigen, anti-delta IgM, anti-delta total titer, anti-HCV, anti-CMV IgM, anti-HSV IgM, anti-EBV IgM were performed when patients serum ALT and/or AST levels were elevated. Liver biopsy specimens were obtained using Menghini needle, when clinically indicated.

Laboratory methods: Hepatitis B markers, IgM anti-HAV, anti-HDV, anti-CMV, anti-HSV, anti-EBV were tested by enzyme-linked immunoassays using commercially available kits. HBV DNA was detected by hybridization method. Anti-HCV was assayed by Ortho HCV antibody ELISA system. Positive results were confirmed by RIBA. Serum biochemistry was determined by sequential multiple autoanalyzer.

The etiology of acute hepatitis was attributed to superinfection with other viral agents if releavent serological viral markers (delta antigen, anti-delta, anti-HCV, anti-HAV IgM, anti-CMV IgM, anti-HSV IgM, anti-EBV IgM) were became positive during acute episode or follow-up. NonA, nonB superinfection was suspected if there was a transient decrease of HBV DNA in the acute phase without evidence of other known non-B virus infection, or if the patients were negative for HBeAg, HBV DNA and other non-B viruses during both acute and convalescence phases (4). The episodes of acute hepatitis were suspected to represent immune clearence of HBeAg in the natural history of chronic HBV infection if the patients were initially HBeAg positive with or without HBV DNA in serum, and then became negative for HBeAg and HBV DNA during follow-up (5,6). The diagnosis of spontaneous reactivation of hepatitis B in a patient who previously had IgG anti-HBe and anti-HBe is based on demonstrating the reappearence of IgM anti-HBe and/or the seric markers of viral active replication, namely HBeAg and HBV DNA (7,8). If the patients had been initially HBeAg and HBV DNA seropositive and acute episode of hepatitis was with increasing titers of HBV DNA, these attacks were also attributed to the spontaneous reactivation of chronic HBV infection (8,9). Hepatocellular carcinoma (HCC) was diagnosed by radiological means.

All liver biopsy specimens were fixed in 10% formalin and stained with hematoxylin-eosin.

Statistical Analysis. Statistical analyses were conducted using Student's t test and chi-square test, where appropriate.

RESULTS

Fourty patients (30 males, 10 females; mean age: 38.5±15.4 years) with acute episode of acute hepatitis (mean ALT: 766.1+693,9 RFU, mean AST: 510.0±435.3 RFU, mean bilirubin: 4.0±4.6 mg per deciliter) superimposed upon chronic HBV Infection were studied. The releavent etiologies of these episodes are shown In figure 1-3.

The etiological and biochemical data of HBeAg seropositive and anti-HBe seropositive patients are listed in Table 1 and Table 2, respectively.

The biochemical changes In the two groups of patients during their exacerbations were comparable ($p>0.05$). Forty per cent of acute exacerbations in both groups were related to superimposed viral infections. The loss of HBeAg and seroconversion to anti-HBe was considered to be responsible for 5 of 15 (33%) of the acute exacerbations among patients seropositive for HBeAg. Fifty-six per cent of acute episodes in anti-

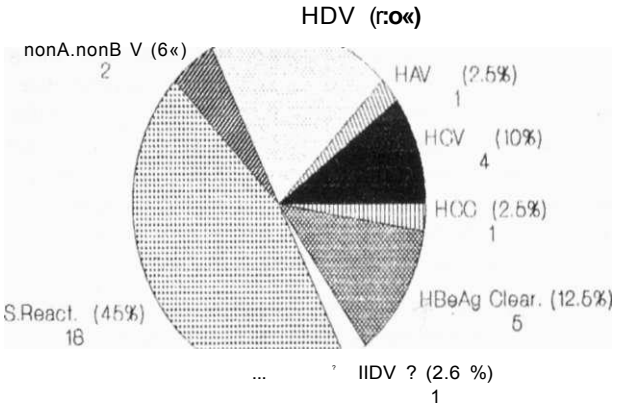

Figure 1. The releavent etiologies of acute episodes in overall patients (n=40).

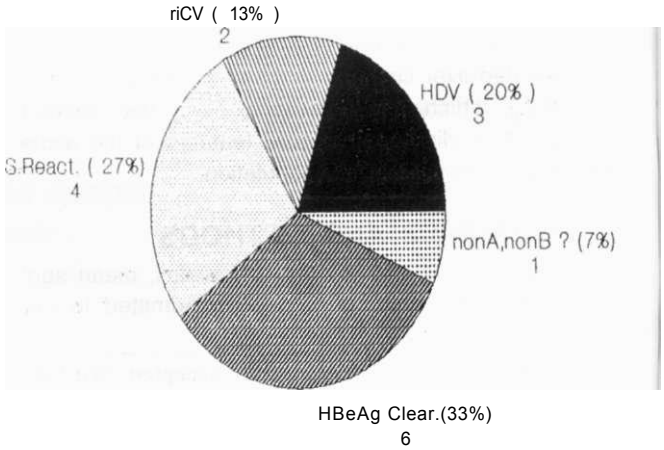

Figure 2. The releavent etiologies of exacerbations in HBeAg seropositive patients (n=15).

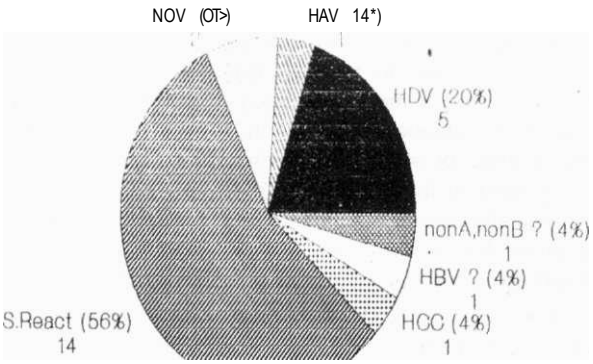

Figure 3. The releavent etiologies of acute episodes in anti-HBe seropositive patients (n=25).

HBe positive patients and 27% of the exacerbations in HBeAg positive patients were associated with reactivation of HBV infection. In one patient, acute attack was with IgM anti-HBc and concurrent HBsAg and anti-HBs seropositivity and dual HBV infection was suspected.

There was no statistically significant difference for biochemical variables between each group constituted according to etiological considerations (p>0.05).

Acute episodes were asymptomatic in one patient, while, associated with symptoms mild to severe in others. In four^patients with established compansated cirrhosis, attacks led to decompensation. Exacerbations were with subfulminating course in three patients in whom they were attributed to spontaneous reactivation of hepatitis B, delta superinfection and clearence of HBeAg, respectively.

Among anti-HBe seropositive patients, two patients were found to be IgM anti-HSV and one patient IgM anti-CMV seropositive during acute attacks which were attributed to spontaneous reactivation, HDV superinfection and HCV superinfection, individually. These findings were thought to represent reactivation of latent infection during acute episode rather than the primary etiological factors. Clinical and histological features were not consistent with either HSV hepatitis or CMV hepatitis in these patients.

DISCUSSION

Acute episode of hepatitis is a common occurence during the course of chronic hepatitis B virus (HBV) infection (9-12). These acute episodes may be asymptomatic, as observed in one of our chronic active hepatitis patients with spontaneous reactivation of hepatitis B, and are realized by abrupt elevations in serum transminase levels on sequential blood tests. Alternatively, exacerbations may present as clinical attacks of acute hepatitis which were the case in most of the patients in these study. These attacks were the first manifestations of previously asymptomatic chronic HBV infection in three patients and misdiagnosed as acute hepatitis B prior to evaluation of serum protein electrophoresis and liver biopsy specimens.

The results of this study revealed that, of the acute hepatitis superimposed upon chronic HBV infection, more than a third could be attributed to superinfection with other viral agents in this country.

Solely, one episode of acute exacerbation was due to superimposed acute hepatitis A. This is probably due to the endemicity of HAV infection in Turkey with the majority of the people being infected subclinically early in the life.

Table 1. Acute exacerbations in HBeAg(+) Positive patients. (N:15 (37.5%), 5 females, 10 males, mean age: 32.7±10.6yrs)

	No.	Age (yrs)	ALT (RFU)	AST (RFU)	Bilirubin (%mg)
Delta sup.	3	26.3±3.8	669±247.3	242.7±57.6	1.9±1.0
HCV sup.	2	38.5±24.7	411 ±244.7	324±56.6	1.3±1.2
React. HBV	4	29±10.4	1209±1020	501.8±333.7	1.6±1.2
Clear. HBeAg	5	34.4±6.3	939.4±1073	695.6±761.6	3.7±4.9
nAnB? sup.	1	47	312	194	2.0

Table 2. Acute exacerbations in Anti-HBe (+) patients. (N:25 (62.5%), 5 females, 20 males, mean age: 42±17 yrs)

	No.	Age (yrs)	ALT (RFU)	AST (RFU)	Bilirubin (%mg)
Delta sup.	5	35.8±14.2	550.8±312	400.6±417.1	3.0+5.2
HCV sup.	2	23.0+5.7	441.5±210	203.5±38.9	1.3+1.2
HAV sup.	1	23	2039	1193	10.0
HBV? sup.	1	57	283	188	0.65
nAnB? sup.	1	38	363	383	8.35
React. HBV	14	46.0±17.4	781.4+698.8	622.8±437.0	6.0±5.5
HCC	1	62	308	481	4.15

The rate of delta superinfection was similar in HBeAg and antiHBe seropositive groups (3/15, 20% and 5/25, 20%, respectively). Delta infection is endemic in Turkey (3,14). HDV superinfection of an asymptomatic HBV carrier can be confused with acute hepatitis B when the HBV carrier state is not previously suspected, unless appropriate testing is done to demonstrate primary HDV infection (anti-HD Ag IgM and IgG seroconversions) and to suggest that HBV infection is chronic (negative anti-HBe IgM and positive anti-HBe IgG in an HBsAg positive patient) (15,16) as was the case in two of our patients.

Hepatitis C virus did account for 10% (4/40) of the acute hepatitis superimposed upon chronic HBV infection. Three of these patients were suffering from chronic renal failure and under hemodialysis treatment which is a well-known risk factor for HCV infection (17).

Spontaneous reactivation should be considered as a likely diagnosis in any patient with chronic type B hepatitis who develops an unexplained acute hepatitis. In our study, it was more prevalent in antiHBe seropositive group (27% versus 56%). In anti-HBe seropositive group, the diagnosis of reactivation based on demonstrating the reappearence of IgM anti-HBe in a patient who previously had IgG anti-HBe (7,8). In this group, 29% (4/14) of the patients were HBV DNA positive and increase in seric DNA titers were observed. In other patients of this group, we couldn't demonstrate the reappearence of the markers of hepatitis B viral replication, despite seropositivity for antiHBc-IgM. This may be related to the fact that; sometimes the phase of viremia can be very transient, there is no seroconversion to HBeAg, the serum HBV DNA soon becomes undetectable. In such cases, the HBV-DNA analysis in the liver tissue can lead to a correct diagnosis (18). In HBeAg seropositive patients, the reactivation was with increased titers of HBV DNA and anti-HBe IgM seropositivity.

In one of our patients, reactivation of hepatitis B (the reappearence of IgM anti-HBe) was with concurrent HBsAg and anti-HBs seropositivity. However, the possibility of reinfection by a virus of different HBsAg subtype couldn't be excluded as we were not able to determine HBsAg and antibody specifity. Liver histology progressed from CPH to CAH and anti-HBs titers progressively decreased and disappeared during follow-up.

All hepatitis B surface antigens (HBsAg) appear to possess a common, group-reactive determinant, a, plus, additional, allelic determinants d/y and w/r (19). After exposure to the hepatitis B virus the antibody produced (anti-HBs) is primarily of anti-a specifity which renders people immune to rechallenge with HBV. Less often, individuals will develop, in addition, other specific antibodies appropriate to the subtype to which they have been exposed (20).

Hepatitis B surface antigen and anti-HBs concurrence may be heterotypic or homotypic (21). This finding may be due to passive transfer of nonspecific antibodies (22); it may be related to exposure to HBV of different subtype specifities (23), or it may be the consequence of a disturbance in immunologic control mechanisms of these patients, especially of those with histologically advanced disease, which may result in the production of a wide variety of antibodies that do not influence the course of the disease (24,25).

If serum markers of HBV reactivation are negative and superinfection of another known hepatotropic virus is excluded, HBV reactivation may be mistaken for non A, non B infection. However, superinfection with non A, non B viruses is usually with decrease in the titers of HBV markers in spite of, anti-HBe IgM seropositivity in reactivation of chronic type B hepatitis (4,26). In two of our patients, one with HBeAg seropositivity and another with anti-HBe seropositivity, and without apparent cause for acute exacerbation, these episodes might be due to superinfection with non-A, non-B hepatitis virus (es). However, transient changes in HBV replicative state, that we missed can't be ruled out.

Acute episode of hepatitis was related to the clearence of HBeAg, in a third (5/15) of the HBeAg seropositive patients. In a study from Taiwan, HBeAg clearence occured in 74 of 237 (31%) HBeAg-positive patients with chronic hepatitis over a 6 to 72 months follow-up period (mean 24.5 months) (27). An increase in ALT to greater than 300 IU preceding the HBeAg clearence was found in 62 per cent of patients.

Acute hepatitis associated with clearence of HBeAg is almost always associated with an exacerbation of hepatic inflammation and on occasion, results in marked deterioration of symptomatic state (28). The reported annual rates of conversion of HBeAg to anti-HBe in hepatitis B carriers have been from 3 to 25 per cent per year (5,8,10,20,29). Presumably the flare in hepatitis occuring during the clearence of HBeAg is the result of a more effective attack by cytotoxic T lymphocytes on the infected hepatocyte.

In conclusion, about a third of the acute hepatitis superimposed upon chronic HBV infection was the result of superinfection with other non-B viruses, more than half of which were due to HDV superinfection, whereas roughly two-thirds were due to changes in HBV activity state (spontaneous inactivation and reactivation of HBV replication). There was no discernible difference between HBeAg positive and anti-HBe positive patients in regard to superinfection with other non-B viruses, clinicopathological and biochemical features. Further and more expanded studies with more prolonged follow-up are needed to delineate the incidence of acute exacerbations in distinct subgroups of chronic HBV infection in Turkey and the role(s) of the other nonA, nonB, nonC viruse(s).

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