

Anti-hepatitis delta virus seroprevalence and risk factors in patients with hepatitis B in Southeast Turkey

Mustafa K. Celen, MD, Celal Ayaz, MD, Salih Hosoglu, MD, Mehmet F. Geyik, MD, Mehmet Ulug, MD.

ABSTRACT

Objective: To obtain regional epidemiological data on hepatitis delta virus (HDV, a defective virus) infections, the incidence of anti-HDV positivity and the associated risk factors in asymptomatic hepatitis B virus surface antigen (HBsAg) carriers and in patients with chronic active hepatitis B.

Methods: The study took place at Dicle University Hospital (Diyarbakir, Southeast of Turkey) between January 2002 and July 2004. Anti-HDV screening was performed in asymptomatic hepatitis B carriers (N=889) and in patients with chronic active hepatitis B infection (N=120). We explored the association between anti-HDV positivity and asymptomatic hepatitis B carrier status, presence of active hepatitis B, age, gender, the durations of HBsAg positivity and hepatitis B e antigen (HBeAg) positivity.

Results: In 6% of asymptomatic hepatitis B carriers (53/889) and in 27.5% of patients with chronic active hepatitis B (33/120) anti-HDV was positive. The incidence

of anti-HDV positivity was significantly higher in patients with chronic active hepatitis B compared with asymptomatic carriers ($p<0.001$). A significant association between the duration of HBsAg carrier status (3.2 ± 1.4 years) and anti-HDV positivity was also found ($p<0.001$). Age, gender, and HBeAg positivity were not significantly associated with anti-HDV positivity ($p>0.05$).

Conclusion: Anti-HDV positivity was significantly more common in patients with chronic hepatitis B compared with asymptomatic hepatitis B virus (HBV) carriers in a region with a high prevalence of HBV infection. We found a significant relationship between the duration of HBsAg carrier status and anti-HDV positivity, however, age, gender, and presence of HBeAg were not significantly associated with the development of anti-HDV positivity.

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Hepatitis delta virus (HDV), which was first defined by Rizzetto in 1977 in Italy, is a defective RNA virus that lacks pathogenicity on its own. It requires the presence of hepatitis B virus surface antigen (HBsAg) for replication. Following its replication in the nucleus of the hepatocyte, it is transferred to cytoplasm, where it is enveloped by HBsAg and secreted into the circulation.¹ Hepatitis delta virus is a

member of the viral sub-family referred to as satellites and has co-infected more than 10 million people who are infected by hepatitis B virus (HBV).² Clinically delta infection manifests itself as a co-infection or a superinfection. In co-infection, both HBV and HDV are responsible for the acute infection. This form of the disease spontaneously resolves in the majority of the cases, with 5% developing chronic disease and

From the Department of Clinical Microbiology and Infectious Diseases, Dicle University Hospital, Diyarbakir, Turkey.

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Address correspondence and reprint request to: Dr. Mustafa K. Celen, Dicle Universitesi Hastanesi, Klinik Mikrobiyoloji ve Enfeksiyon Hastalıkları Anabilim Dalı, 21280, Diyarbakir, Turkey. Tel. +90 (412) 2488006. Fax. +90 (412) 2488440. E-mail: mkcelen@hotmail.com

the reported mortality is between 2% and 20%. In superinfection, additional HDV infection develops in an HBsAg carrier. In this form, the risk of developing chronic disease is high (50-70%) with accompanying risks of chronic active hepatitis and cirrhosis.³ Chronic hepatitis B virus infection (65.7%) was the most frequently identified risk factors for hepatocellular carcinoma in Turkey.⁴

Hepatitis delta virus accounts for 3-25% of fulminant hepatitis cases. The most important difference between superinfection and co-infection is the higher rate of chronicity and cirrhosis following the acute infection in the former.⁵ The reported figures for HBsAg seroprevalence in our geographical region is 8.9% for the period between 1988 and 1991⁶ and 4.9% for the year 2003.⁷ In contrast to sufficient amounts of data regarding HBV infections for our region, data regarding HDV infection is scarce. Therefore, we assessed the anti-HDV prevalence in HBsAg carriers and in patients followed for chronic active hepatitis B.

Methods. Between January 2002 and July 2004, anti-HDV screening was performed at the Department of Infectious Diseases Clinical Microbiology Unit, Dicle University Hospital, Diyarbakir, Turkey in a total of 889 patients with asymptomatic hepatitis B carriers and 120 patients followed with a diagnosis of chronic active hepatitis B (total of 1009 patients with HBsAg positivity). Patients with isolated HBsAg positivity during the previous 6 month period were considered as asymptomatic hepatitis B carriers. The diagnosis of chronic hepatitis B was based on HBsAg positivity (6 months), a measured ALT level of 1.5 times the upper limit of normal on 2 different occasions or 2 times the upper limit of normal in a single assessment, serological parameters, ultrasonography findings, and liver biopsy. Macro-enzyme-linked immunoabsorbent assay (ELISA) (Roche Diagnostics Corporation, Indianapolis, IN, USA) and micro-ELISA (Diapro, Diagnostic Bioprobes Srl Via Columella, Milano, Italy) methods were used for HBsAg (macro-ELISA) and anti-Delta (micro-ELISA) assessments. Patients were initially divided into the following 2 groups: HBsAg carriers (group 1), and patients with chronic active hepatitis B (group 2). The association between anti-HDV positivity and asymptomatic hepatitis B carrier status, presence of chronic active hepatitis B infection, age, gender, the duration of HBsAg positivity, and hepatitis B e antigen (HBeAg) positivity were explored.

Statistical analyses were performed with the Statistical Package for Social Sciences version 10.0 software. A *p* value less than 0.05 were considered significant.

Results. In group I, consisting of asymptomatic hepatitis B carriers, 523 patients (58.8%) were male and 366 (41.8%) were female. The mean age was 38.2 ± 18.2 years for males and 33.9 ± 13.9 years for females. Anti-HDV positivity was detected in 6% (53/889) of these cases. In group 2, consisting of patients followed for chronic active hepatitis B, 69 (57.5%) were female and 51 (42.5%) were male. The mean age in female patients was 32.5 ± 15.4 years and 39.1 ± 18.9 years in male patients. Of these patients, 27.5% (33/120) were anti-HDV positive. Overall, the prevalence of anti-HDV positivity among 1009 patients was 8.5% (86/1009). Anti-HDV positivity was significantly more common in patients with chronic active hepatitis B infection compared to asymptomatic carriers ($p < 0.001$).

Among asymptomatic HBV patients, the average duration of HBsAg carrier status was 3.2 ± 1.4 years for anti-HDV (+) and 2.2 ± 1.2 years for anti-HDV (-) patients. In patients with chronic active hepatitis B infection, the corresponding figures were 3.4 ± 1.1 years for anti-HDV (+) and 2.2 ± 0.9 years for anti-HDV (-) patients. The relationship between the duration of HBsAg carrier status and anti-HDV positivity was statistically significant ($p < 0.001$). Of the 53 asymptomatic HBsAg carriers with anti-HDV positivity, 23 (43.4%) were female and 30 (56.6%) were male. The mean age for female patients was 37.2 ± 11.4 years and 34.8 ± 10.7 years for male patients. Among 33 patients with chronic active hepatitis B infection and anti-HDV positivity, 19 (57.6%) were female and 14 (42.4%) were male. The mean age for female patients was 34.8 ± 10 years and male patients were 35 ± 13.1 years. The age and gender were not associated with the presence of anti-HDV positivity ($p > 0.05$) **Table 1.**

Of the 889 asymptomatic HBsAg carriers, 484 (54.4%) were HBeAg (+), while among 120 patients with chronic active hepatitis B, 71 (59.2%) were HBeAg (+). Again, presence of HBeAg was not significantly associated with anti-HDV positivity ($p > 0.05$).

There was a significant association between the duration of HBsAg carrier status and anti-HDV positivity ($p < 0.001$). However, age, gender and HBeAg positivity were not significantly associated with anti-HDV positivity ($p > 0.05$).

Discussion. The reported incidence of anti-HDV seropositivity among HBsAg carriers shows a great variation, ranging from 4.1-25.6% at different regions of the world.⁸⁻¹⁰ In our country, the reported incidences of anti-HDV positivity among healthy carriers and in

Table 1 - Distribution of anti-HDV (+) patients by age, gender, HBeAg positivity, duration of HBsAg positivity, and the characteristics of hepatitis B infection.

Risk factors	Anti-HDV	Anti-HDV	P-value
	(+)	(-)	
Asymptomatic carrier	53	836	>0.05
Chronic active hepatitis	33	87	0.001
Duration of HBsAg positivity in carriers (years)	3.2 ± 1.4	2.2 ± 1.2	<0.05
Duration of HBsAg positivity in chronic HBV infection	3.4 ± 1.1	2.2 ± 0.9	<0.05
HBeAg positivity	555	454	>0.05
Age	35.5 ± 11	35.4 ± 11.4	>0.05
Gender (male/female)	44/42	530/393	>0.05
Total	86	923	
HBsAg - hepatitis B virus surface antigen, HDV - hepatitis delta virus, HBV - hepatitis B virus, HBeAg - hepatitis B e antigen			

patients with chronic hepatitis B carriers differ between 3% and 15.7%.^{11,12} Considerable epidemiological data exist regarding HBV in our region, while information about HDV carriage is lacking.

In Turkey, the reported incidence of anti-HDV positivity among patients with chronic hepatitis B infection range from 15.6-41.2%.^{13,14} In the present study, 33 (27.5%) of the 120 patients with chronic active hepatitis B infection were anti-HDV positive. Again in Turkey, the reported co-infection rates in patients with acute hepatitis B are between 3.8% and 17.9%,^{15,16} while the local co-infection rates reported for Southeastern Turkey are between 7.3% and 21.8%.⁵ In a previous study in Diyarbakır region, 4 (6.2%) out of 65 patients with acute hepatitis B had HDV co-infection.¹⁷

Sahan et al¹⁸ examined the frequency of anti-HDV in 1223 asymptomatic HBsAg carriers (mean age: 35.8 years; 674 [55.1%] male, 549 [44.9%] female) between 1998 and 2004. In that study, the average duration of HBsAg carrier status was 55 months and 40 patients (3.2%) were anti-HDV positive.¹⁸ In the present study, 53 patients (6%) were anti-HDV positive. The duration of HBsAg carriage was 3.2 ± 1.4 years in anti-HDV (+) and 2.2 ± 1.2 years anti-HDV (-) patients, with a significant association between the duration of HBsAg carriage and the presence of anti-HDV positivity ($p < 0.05$), as reflected by increased likelihood of anti-HDV positivity in patients with longer duration of HBsAg carriage.

In a study from Ankara, 6 (9.5%) of 63 patients with chronic hepatitis B infection were anti-HDV positive.¹⁹ Other studies, which were carried out by

Oguz et al²⁰ the ratio of anti-HDV seropositivity in chronic hepatitis B patients were determined as 33%, and Turfan et al²¹, determined it as 51.8% in our country. In our study, anti-HDV was positive in 33 (27.5%) of 120 patients with chronic hepatitis B infection. In our region, the frequency of anti-HDV positivity was higher compared to other geographical locations of Turkey.

Al-Traif et al⁸ investigated HBsAg positivity in 19250 blood donors, and found HBsAg positivity in 780 (4.1%), 67 (8.6%) of whom were also positive for anti-HDV. In their study, investigators did not differentiate between acute, chronic or asymptomatic patients. In our study, 86 (8.5%) of 1009 HBsAg positive patients were anti-HDV positive. Therefore our results bear more resemblance to those reported from Saudi Arabia, which is geographically similar to our region.

In a study from Bangladesh (n=180), 21.8% of asymptomatic HBsAg carriers and 25.6% of symptomatic hepatitis B patients were anti-HDV positive.⁹ In our study the frequency of anti-HDV was 6% for asymptomatic HBsAg positive patients and 27.5% for patients with chronic active hepatitis B. On the other hand, in a study from India, anti-HDV was screened in 238 HBsAg positive patients, and 5.7% of patients with chronic viral hepatitis were anti-HDV positive.¹⁰ Anti-HDV frequency in our study is higher compared to the results from India. In Italy, 50 (7%) of 758 patients with chronic hepatitis B infection were anti-HDV positive,²² again our figures being higher compared to those reported in this multi-center study from Italy.

In Bangladesh, asymptomatic and symptomatic groups had similar anti-HDV positivity rates, while in our study, the frequency of anti-HDV positivity was significantly higher in patients with chronic hepatitis B infection ($p = 0.001$).

The vaccination of hepatitis B was applied to children from 0 month in routine vaccination program of the Ministry of Health since 1998, in our country. Appearing of the efficacy of this program is yet early, however, we can see the efficacy after this decade in our region where hepatitis B has been frequently spreading in the family. In the study of Felek et al,²³ which was reflected the period before the vaccination program, anti-HDV seropositivity was 8.5% in asymptomatic hepatitis B carriers in our region. This ratio was determined as 6% in our study. Results were similar; we can draw a conclusion that so the efficacy of this program has appeared early.

Our experience in hepatitis delta treatment with interferon- α or peg-interferon- α were not successful.

The sustained virological response was in both groups 10.7% and 14.2%.

In conclusion, in this study from Southeastern Turkey, where a high prevalence of HBV infection exists, the frequency of anti-HDV positivity was significantly higher compared to that in asymptomatic HBV carriers ($p=0.001$). The duration of HBsAg carrier status was significantly associated with anti-HDV positivity ($p<0.05$), while there was no significant relationship between the development of anti-HDV positivity and age, gender, and presence of HBeAg. The rate of anti-HDV positivity was 6% and 27.5% in asymptomatic hepatitis B carriers and in patients with chronic hepatitis B infection. This is the first study to provide data on HDV infection in our geographical region.

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