

Seroprevalence and Risk Factors of Hepatitis Delta Virus in Chronic Hepatitis B Virus Infection in Zahedan

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Abstract- Hepatitis delta virus (HDV) infection results in more severe and even fulminant form of hepatitis B in co-infected cases. This study was designed to estimate the prevalence of anti-HDV positivity and the associated risk factors in patients with chronic hepatitis B virus infection in Zahedan (Iran). In this cross-sectional study a total of 440 consecutive patients with chronic hepatitis B virus (HBV) infection attending the Zahedan Gastroenterology and Hepatology clinics from 2008 to 2011 were included. We performed test for HDV serum marker, using commercially available enzyme-linked immunosorbent assay kit. Patients were split into two groups according to their HDV antibody status as HDV positive or negative. The collected data were coded, and the statistical analyses were conducted. Four hundred and forty patients with various forms of chronic HBV-related liver diseases enrolled in the study. 200 (45.5%) patients were carrier for HBV. 196 (44.5%) patients had chronic active hepatitis and 44 (10%) patients suffered from cirrhosis. Anti-HDV was demonstrated in 75 patients (17%). The prevalence of HDV was 7%, 16.3% and 65.9% in carriers, patients with chronic active hepatitis and cirrhosis, respectively. HDV infection is still an important public health problem in Zahedan and appears a major cause of progression of liver disease induced by HBV.

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Introduction

Among six known hepatotropic viruses, delta virus or hepatitis D virus (HDV) is a small RNA containing virus requiring concomitant presence of hepatitis B virus (HBV) for its survival and pathogenicity (1). Since discovery of HDV in 1977 by Rizzetto in Italy, it is well documented that HDV is a widespread disease that has affected a large number of population with HBV infection in the world. Delta virus infection results in more severe chronic hepatitis B and occasionally fulminant form of acute hepatitis B in co-infected cases (2,3). This virus has co-infected more than 15 million people who are infected by HBV (4). Hepatitis delta virus accounts for 3-25% of fulminant hepatitis cases (5). Almost, 1.2% to 9.7% of the world's population and approximately 2.14% of the Iranian population have an HBV infection (6). In two last decades, several studies from various geographic of Iran demonstrated that prevalence of HDV ranged from 2.4% to 20.7% (7-11). Therefore HDV is a widespread disease and a health

problem that has affected a large number of populations with HBV infection in Iran. Because absence of the epidemiological features of HDV in southeast of Iran, the aim of this work was to estimate the epidemiological features of HDV infection in a sample of HBV-infected patients in the city of Zahedan, the capital of the province of Sistan and Balouchestan.

Materials and Methods

In this cross-sectional and descriptive study all consecutive patients with chronic HBV infection attending the Zahedan Gastroenterology and Hepatology clinic from 2008 to 2011 were included. Our clinic is situated in the province of Sistan and Balouchestan and serves as the main tertiary care center located in the southeastern part of Iran. For all subjects a face-to-face interview using a questionnaire about demographic characteristics, socioeconomic status, parenteral exposure to blood or blood products, social and sexual behavior, close contacts with HBV infected patient,

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intravenous drug use, tattoos, acupuncture, phlebotomy and dental procedures was performed. All patients were chronic HBV infected and had at least two separate liver function test (LFT) at six month period. Patients were divided into three groups; group one, patients with chronic HBV infection who were in a carrier state (asymptomatic, normal LFT, normal sonography, and negative for HBeAg or HBV-DNA load less than 200-2000 IU/ml) or exhibited immune tolerance (asymptomatic, normal LFT, normal sonography, and HBeAg-positive), group two; patients with chronic active hepatitis (none of those included in group one or three), group three; HBV-related cirrhosis (any marker of portal hypertension or ultrasonographic finding of small and coarse echo liver with round edges). For all patients, demographic data and risk factors were recorded. We performed test for HDV serum marker, using commercially available enzyme-linked immunosorbent assay kit (DiaSorin, Italy). Patients were split into two groups according to their HDV antibody (anti-HDV) status (HDV positive or negative). The collected data were coded and analyzed using SPSS, version 17 (Chicago, USA), using descriptive statistical methods, Chi-square and logistic regression with forward stepwise method (LR).

Results

Overall, 440 cases, comprising 302 men (68.6%) and 138 women (31.4%) with a mean age of 40.5 ± 14.6 years were studied. With regard to mode of diagnosis, the HBV was detected by disease-related follow up in 174 cases (39.55%), familial check-up in 138 cases (31.36%), by individual testing in 12 cases (2.73%), after blood donation in 112 cases (25.45 %) and during pregnancy in 4 patients (0.9%). The distribution of frequencies of risk factors for hepatitis B is shown in table 1.

Overall, seventy five patients (17%) were positive for HDV. Based on chronic hepatitis B stages (carrier, chronic active hepatitis or cirrhosis), HDV frequencies are shown in table 2.

On analysis of demographic and risk factors by

Table 1. Hepatitis B virus infection risk factors frequencies in participants.

Risk factor	Number	Percentage
Positive family history	228	51.8
Tattoo	68	15.45
Phlebotomy	18	4.1
Dental procedures	49	11.13
Transfusion	18	4.1
Health worker	4	0.9
Sexual	4	0.9
I.V. drug abuser	4	0.9
Not identified	108	24.5

logistic regression (in a univariate analysis), age, sex, education and HBV variety had a significant relationship with HDV. However, in a multivariate analysis, only sex and HBV variety were significant. In females, risk of HDV as 0.36 times less than males and in cirrhotic patients risk of HDV was 10.54 times more than carriers. The calculated odds ratios (ORs) with 95% confidence intervals (CI) of various factors are presented in table 3.

Discussion

Our study showed that the overall seroprevalence of HDV in chronic HBV-infected patients was 17%. As expected, the prevalence of HDV was 7%, 16.3% and 65.9% in carrier, chronic active hepatitis and cirrhosis, respectively. However, in our cirrhotic patients this figure is unexpectedly high (65.9%) and to the best of our knowledge, no study has reported such high figure except in a recent study from Quatte, Pakistan (26). Positive family history, tattoo, phlebotomy and dental manipulation were major risk factors for HBV and probably HDV in our subjects. However, many of our patients did not have an identifiable risk factor, probably unsafe injection in the past is responsible for infection in these patients, although, the possibility of missing bias cannot be excluded. In females, risk of HDV as 0.36 times less than males and this finding in our study may be due to high risk behaviors in males than females.

Table 2. HDV positivity based on chronic hepatitis B variety.

Patients	No.	HDV Antibody		P-value
		Positive (No, %)	Negative (No, %)	
Carrier	200	(14, 7)	(186, 93)	0.002
Chronic active hepatitis	196	(32, 16.3)	(164, 83.7)	0.04
Cirrhosis	44	(29, 65.9)	(15, 34.1)	0.4

Table 3. Odds ratios of risk factors of hepatitis D virus infection.

Factor	Unadjusted OR 95% CI	Adjusted OR 95% CI
Age	1.04 (1.01- 1.07)	
Sex		
Male	1.00 (reference)	
Female	2.25 (1.12- 4.52)	
Education		
Illiterate	3.98 (11.67- 9.51)	1.00
High school	1.94 (0.76- 4.92)	0.36 (0.17- 0.77)
University degree	1.00 (reference)	Excluded from model
Risk factor		
History of family	1.00 (reference)	
Not identified	0.91 (0.42- 1.95)	
Tattoo	2.00 (0.71- 5.96)	
Phlebotomy	0.61 (0.07- 5.32)	
Dental procedure	0.58 (0.09- 4.88)	
Chronic hepatitis B stage		
Cirrhosis	10.23 (3.61-29.03)	10.54 (3.5-31.75)
Active chronic hepatitis B	1.44 (0.64-3.22)	1.49 (0.63-3.40)
Carrier	1.00 (reference)	1.00 (reference)

Four risk factor variables (20 cases) were excluded from analysis (8 cases due to transfusion, 4 health worker, 4 cases with history of I.V. drug abuse and 4 cases with risk factor related to sexual behavior) as sample size was not enough for proper statistical analysis. OR: Odds Ratio,

In study of Montazeri *et al.* (12) a significant minority of those with persistently normal ALT that considered as healthy carrier of hepatitis B had moderate to advanced liver disease and therefore relying on traditional criteria for healthy carrier state resulted in missing of some chronic active hepatitis cases as healthy carrier. Therefore, by performing serum HBV-DNA loading, one of the advantages of our study, is relatively accurate classification of various forms of chronic HBV infection (carrier vs. chronic active hepatitis and/or cirrhosis).

Previous studies from different parts of Iran demonstrated 2.2%- 20.7% of hepatitis B subjects have been infected with HDV (7-11,13). In a similar study to our work from Tehran, Foroutan *et al.* (9) reported HDV prevalence in a sample of HBV-infected patients as 12.6%. HDV prevalence base on HBV stage were 1.6%, 20%, 5.6% and 37.2% in asymptomatic carriers, patients with acute hepatitis, chronic hepatitis, and cirrhosis respectively. In 2000, Karimi and colleagues reported that 2.5 % of patients with HBV carrier state infected with HDV (7). Other studies from Tabriz (13,14), Babol (15), Isfahan (16), Golestan (17), Hamedan (18) and Khuzestan (19) reported prevalence of HDV 0.6%, 2%, 2.9%, 5.8%, 17.3% and 11.5% respectively. In Kerman (west neighboring of our province), prevalence of

hepatitis D infection (20.7%) is relatively higher than to our study (8). According to study carried out by Alavian *et al.* in Iran, seropositivity of HDV among HBV-infected patients was 7.8% (10). This means that the prevalence of HDV in Zahedan is higher than Iran's average. Based on the results which have emerged from previous studies in Iran, the rate of HBV infection in Zahedan is higher than that in other provinces (20,21). Therefore, the rate of HDV infection can be high. On the other hand, difference at least in part may be due to different inclusion criteria. In previous studies, a significant proportion of the patients were asymptomatic HBV carriers with normal transaminases contrary to our study in which all those with chronic infection of HBV were included. Since HDV infection is presumed to be associated with an increase in inflammation and progression of liver disease, a higher rate of HDV infection is to be expected in those with chronic active hepatitis and cirrhosis.

In other countries prevalence of HDV is various and based on geographical region up to 5.9% in Switzerland (22) to 23% in Japan (23), and even 0 percent in some regions of Romania (24). Most notably, our results is similar to Pakistan, east neighboring of Sistan and Balouchestan province, this figure 16.3% (25) and in other recent research in Quatte (eastern Pakistan

province and east neighboring of Zahedan) 65.2% (26) were reported, this may in part be due to commute between two country.

In conclusion, like others studies, these findings showed that HDV infection may accelerate liver damage in patients who suffer from chronic hepatitis and cirrhosis. An HDV infection is still an important public health problem in Zahedan and appears a major cause of progression of liver disease induced by HBV. In some countries a declining trend in the prevalence of HDV infection was reported (12,27,28). Organized health care management such as broad-scale vaccination and screening programs, may help to insure that HBV/HDV infection incidence declines in Zahedan in future.

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