

Original Article

Clinical Impact and Frequency of Hepatitis D Virus Infection in HBsAg Positive Patients in a Southern Province of Iran (Kerman)

Zahedi MJ¹, Darvish-Moghaddam S^{1*}, Zareei H¹

1. GI Section, Department of Internal Medicine Afzalipour Academic Health Center, Kerman, Iran.

Abstract

Background and Aims: Hepatitis D virus (HDV) can infect human population either as a superinfection or concurrent hepatitis B virus (HBV) infection. It is expected that presence of HDV infection is more prevalent in endemic HBV areas. Overall 5% of Iranian general populations are chronic HBV carriers. The aim of this study was to determine the seroprevalence of HDV and its clinical impact in a local area of southern Iran (Kerman province).

Methods: The study carried out during 2006-2007 on all hepatitis B surface antigens (HBsAg) positive subjects who referred to the main referral hospital (Afzalipour Academic Health Center) and subspecialty GI offices in the city of Kerman. The study included just stable chronic hepatitis B and inactive HBV carriers around the province. High risk group subjects and other concurrent hepatitis viral infections were excluded.

Results: One hundred and ninety six patients were enrolled in the study. They consist of 143 (73%) men, 53 (27%) women, with a mean age of 39.2 ± 7.1 (range 20-60) years. Twenty-one subjects (10.7%) were positive for anti HDV antibody (Ab). Male to female ratio was 6/1 in this group. All of the HDV positive cases acquired the infection as a super-infection. Elevated aminotransferases (ALT- AST) was documented in 81% of HDV positive cases and in 41% of HDV negative subjects ($p=0.001$).

Conclusion: HDV investigation is recommended in HBV infected patients, particularly those with elevated liver enzymes in a relatively high prevalent area as in Iran.

Keywords: Hepatitis D Virus; HBsAg; Kerman; Iran

Introduction

Hepatitis D virus (HDV) can infect human population only in the presence of hepatitis B virus (HBV). Worldwide it is estimated that overall 5% of hepatitis B surface antigen (HBsAg) positive carriers are infected with HDV. Seroprevalence of HDV changed during the last two decades in some

geographical areas, specially a declining trend in southern parts of Europe was observed (1, 2). However the prevalence of HDV differs among different nations.

In a report from Bangladesh, the seropositivity for HBsAg and anti hepatitis B core (HBc) antibody in asymptomatic healthy children and adults were 3% (16/534) and 21.1% (113/534) respectively. A high rate of co-infection with HDV was observed among HBsAg positive subjects (44/180 =24.4%) in this study (3).

Huo et al from Taiwan have reported a decrease in HDV infection in hepatitis B surface antigen (HBsAg) carriers from 23.7% in 1983 to 4.2 % in 1995 (4). Hou and

*Corresponding author: Sodaif Darvish Moghaddam MD, GI Section, Department of Internal Medicine Afzalipour Academic Health Center, Imam High Way, Kerman, Iran
Fax: (+ 98) 341 322 27 63
Email: sdmoghaddam@yahoo.com

associates also reported the prevalence of HBV and HDV infections in two high risk groups in Taiwan in 2003. They found the positive serologic markers for HBV and HDV in 494 intravenous (IV) drug users to be 18%, and 5% and in 916 female prostitutes to be 12% and 5% respectively (5). In Chakraborty study from India, evidence of HDV infection was demonstrated in 10.6% of hepatitis B virus (HBV) related liver diseases (6).

According to previous studies, overall 35% of Iranian general populations show a trace of HBV exposure (HBcAb positive) and 5% of them are HBsAg positive (7). Some studies in Iran, have shown a seroprevalence of 2.4-14% of HDV in otherwise healthy HBsAg carriers (8-11). This cross sectional study was carried out to evaluate the seroprevalence and clinical impact of HDV infection in HBsAg positive subjects in Kerman.

Methods

The study performed during a one year period (2006-2007) on HBsAg positive patients who referred to Afzalipoor hospital and outpatient gastrointestinal (GI) clinic in Kerman. Because of a referral status for the teaching hospital (Afzalipoor Academic Health Center) and the subspecialty GI offices, the enrolled patients were from the whole province. Patients demographic data, history and physical examination were recorded to discover the stigmata of liver disease. The enrolled cases agreed to participate in the study.

In order to reduce the overestimation of HDV involvement, we excluded the patients with evidence of extreme presentations of HBV related diseases notably advanced chronic or acute liver events. Therefore, all of the established cirrhotic patients confirmed by histology and/or stigmata of portal hypertension diagnosed by ultrasound and endoscopic findings as well as those suffering from hepatocellular carcinoma and fulminant hepatic failure were excluded from the study. Those subjects with concurrent positive hepatitis C virus (HCV) or HIV infection were excluded as well. High risk groups including hemophilia, blood dyscrasia, regularly

receiving blood, chronic renal failure, hemodialysis and/or peritoneal dialysis, any underlying malignancy and intravenous drug users were also omitted.

Anti HDV antibody (Ab), total and IgM were measured quantitatively by enzyme linked assay (ELISA), using the DIASORIN kits (Italy). Hepatitis B core antibody (HBcAb) including total and IgM type were measured by ELISA method using the Behring kits (Germany) on sera of anti- HDV Ab positive patients to differentiate co-infection (+IgM anti-HBc) from super-infection (-IgM anti-HBc) types of HDV. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by a standardized kit with a normal range of 0-40 IU/L. All of patients with abnormal ALT-AST results were investigated for concurrent additional diseases such as HCV, HIV infection, non-alcoholic steatohepatitis, autoimmune hepatitis, Wilson disease and hereditary hemochromatosis. History of multi-partner sexual contact, medications and alcohol drinking were also recorded in a self-administered questioner.

Statistical analysis

The X² test was used to determine the significance of differences in the prevalence of HDV by age, sex and AST- ALT level. A P value less than 0.05 was considered as statistically significant.

Results

During a one year period, 196 selected patients out of 234 HBsAg positive subjects were enrolled in this study. They consist of 143 (73%) men, 53 (27%) women, with a mean age of 39.2 ± 7.1 (range 20-60) years. The frequency of HDV infection in males were more than females in the studied subjects, however no statistically significant difference was observed between the two groups ($p=0.164$) (Table 1).

Twenty-one subjects (10.7%) were positive for anti HDV Ab (Diagram 1). Male to female ratio was 6/1 in this group. Regarding the HDV involvement, no significant difference was observed among different age groups

Table 1: Characteristic features of HBsAg + subjects based on HDV status

characteristics	HDV positive	HDV negative	Total(No)	p-value*	Odds ratio (CI 95%)
Sex Frequency(%)					
Male	18(86)	125(71)	143	0.164	2.4(0.67-8.50)
Female	3(14)	50(29)	53		
Age (year) Mean±SD	35.6 ± 5.4	41.4 ± 8.3			
Frequency (%)					
20-39 (y)	11(52)	82(47)	93	0.632	1.21(0.49-3.01)
40-60 (y)	10(48)	93(53)	103		
AST-ALT level Frequency(%)					
Normal	4(19)	103(59)	107	0.001	6.08(1.96-18.82)
Elevated	17(81)	72(41)	89		
HBV condition Anti HBC IgM(-)	21	—	—	—	—
Anti HBC IgM(+)	0	—	—	—	—

*: X2 test

($p=0.632$) (Table 1). Among 175 patients infected only with HBV, 103 (59%) cases had normal ALT-AST, while 72 (41%) patients had increased ALT-AST. On the other hand 17 cases (81%) (15 male and 2 female) out of 21 HDV positive patients showed increased ALT-AST levels ($P= 0.001$)(Table 1). None of the anti HDV Ab positive cases had anti Hbc IgM Ab which represents chronically involved HBV cases (super-infection) (Table 1). Among concurrent HBV-HDV positive patients 8 men and 1 woman (43%) were positive for anti HDV IgM Ab, representing an acute process. The remaining twelve (10 male and 2 female) cases were positive for total anti HDV Ab while negative for anti HDV IgM antibody. None of the patients with elevated ALT-AST were affected with additional concurrent diseases. History for taking drugs, drinking alcohol or high risk sexual behavior were not present in the studied subjects.

Discussion

In the present study the prevalence of HDV infection among HBsAg positive patients was 10.7%. In order to avoid over estimation of HDV prevalence, the study was carried out on otherwise chronically stable HBsAg positive patients regardless of aminotransferase levels. The male female ratio was 6. Most of the HDV infected cases (81%) had increased aminotransferases [$P= 0.001$], (Table 1). All of the HDV positive cases acquired the virus following a chronic HBV background (super-infection).

It is estimated that over 35% of Iranians have been exposed to the HBV and about 5% are chronic carriers, ranging from 1.7% in Fars Province to over 5% in Sistan and Balouchestan. It appears that 8% of Iranians infected with HBV will become chronic carriers (7). According to the studies during 1990s in Iran, 2.4-14% of otherwise healthy HBsAg carriers are infected with the HDV (8-

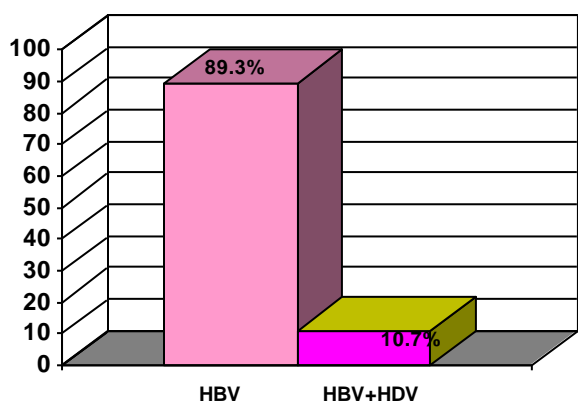


Diagram 1: Frequency of Hepatitis D virus infection in HBsAg positive patients

10). In a general population based study in Hamedan province, located in the west part of Iran, the prevalence of HDV infection, was 2.4% in HBsAg positive cases (8). In Rezvan study, the rate of anti-HDV positivity was 2.5% in asymptomatic chronic HBsAg carriers and 44.5% in HBsAg positive hemodialysis patients (9). In a recent published study from the northeastern part of Iran (Golestan province) based on general population, prevalence of HDV infection was 5.8% among HBsAg-positive cases (11). Compared to the above studies, results of the present study showed a higher prevalence of HDV infection in Kerman part of Iran. This difference is largely due to subjects chosen as the studied population, namely general population vs. HBV positive cases. Seroprevalence of HDV did not significantly differ between age groups in the present study as well as in Roshandel *et al* study (11).

The overall the rate for HBsAg carriers in most parts of Asia was reported to be 4-7% in the general population, but information on the prevalence of HDV infection in these high HBV prevalent areas remain incomplete (12). Several reports indicated a declining trend in the occurrence of HDV infection in some geographical areas especially in Southern Europe. For example, the prevalence of HDV seropositivity (anti-HDV) among HBsAg carriers with liver disease, declined from 25% in 1983 to 14% in 1992 in Italy (2), and from

15.1 to 7.1% in Spain during the same time period (1).

Reports after 2000 from some parts of Europe also have shown epidemiological changes in HDV seroprevalence i.e. 8% in Italy (13), 7.1% in Spain (14), and 3.9% in north-eastern Poland (15).

Hou et al findings also indicated a declining prevalence of HCV and HDV infections among high risk group subjects i.e. IV drug users and prostitutes from 1985 to 2001 in Taiwan (5). A high rate (24.4%) of HDV seroprevalence was observed among HBsAg-positive subjects in a study from Bangladesh (3). Positive HDV cases in HBV infected patients in a national survey report from Pakistan was 16.6% (16), while this figure in a local endemic community in southern Taiwan was 15.3% (17). In a study from Mongolia, the prevalence of positive HBsAg cases among 249 apparently healthy individuals was 10% which 83% of whom were positive for HDV RNA (18).

Our results are similar to those of Nakasone study in Myiako Islands from Japan, where they reported HDV prevalence rate to be 10.6% in 196 chronic HBV carriers (19). Chakraborty et al also determined the HDV prevalence as high as 10.6% in 123 patients with HBV-related liver diseases in a hospital based study in India in 2005. In this study all patients with HBV-related liver diseases comprising of acute viral hepatitis, fulminant hepatic state, chronic hepatitis, cirrhosis and hepatocellular carcinoma were enrolled, while our study included just chronically stable patients (inactive carriers or chronic hepatitis subjects) (6).

The male to female ratio in our study was 6. In the previous reports from Italy (20), Pakistan (16) and Taiwan (17), male gender was an independent factor associated with HDV infection. One possible explanation for the male predominance could be the higher confrontation of men with more hazardous jobs and invasive procedures in developing countries. However injecting drug abusers in the developed countries may explain the higher prevalence of HDV among HBsAg positive subjects as shown in earlier studies from Italy

(2, 20). Sexual transmission may be another possible explanation in young men, however a statistically significant difference regarding the age groups was not observed in our study. It might be explained by the predominant route of transmission via vertical or childhood HBV exposure. Based on the results, all of the cases in our study acquired HDV infection following a chronically HBV state (super-infection). In addition none of these cases had high risk sexual behavior.

Although, 'healthy HDV carriers' have been described, HDV may be potentially more dangerous than other hepatotropic viruses. HDV super-infection, invariably leads to cirrhosis (20). In Nakasone report, higher prevalence of HDV was correlated with severity of underlying liver disease, notably 10.6% in asymptomatic carriers, 32% in chronic hepatitis cases and 40% in liver cirrhosis (20). Most of HDV positive cases (81%) in our study had elevated liver enzymes that are in concordance with previously reported results. In Mumtaz et al study, delta virus infected patients had less severe clinical liver disease compared to delta negative, hepatitis B patients. It might be that they included all of the out-patient and in-patient HBV positive cases presented for various reasons including upper gastrointestinal bleeding, ascites, jaundice and porto-systemic encephalopathy (16).

Conclusion

According to the results of this study the frequency of HDV infection in Kerman was 10.7% among HBsAg positive cases. Because 81% of HDV positive patients had elevated liver enzymes, we recommend that HDV investigation in HBV infected patients, particularly those with elevated liver enzymes should be done. On the other hand, by recent general implementation of HBV vaccine for children and adolescents, it is speculated that prevalence of HDV would be declining in near future in Iran. This needs periodic epidemiological investigations.

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