



Sero-Prevalence of Hepatitis D Virus Infection Among Hepatitis B Surface Antigen Positive Patients in Mashhad, Northeastern Iran

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Abstract

Background: Transmission and persistence of Hepatitis Delta Virus (HDV) depends on presence of the hepatitis B surface antigen (HBsAg) envelope proteins. The prevalence of HDV infection has not been reported previously among HBsAg-positive patients in Mashhad, Iran.

Objectives: To evaluate HDV seroprevalence among individuals with HBsAg seropositivity in Mashhad, Northeastern Iran.

Methods: This cross-sectional was performed in Central Diagnostic Lab of Academic Center for Education, Culture, and Research (ACECR), Mashhad, Iran. Based on database of the lab, 606 HBsAg positive patients were tested for anti-HDV antibodies using the enzyme-linked immunosorbent assay (ELISA) during 2016-2017. Chi-square or Fisher's exact tests and T-test were used to analyze the data by SPSS software at a significance level of 5%.

Results: Among 606 HBsAg positive patients including 335 (55.3%) males and 271 (44.7%) females with a mean age of 43.6 ± 14.8 years old, 35 cases (5.8%) were found to be anti-HDV positive. HDV infection was more prevalent among males (6.9%), older patients ($P = 0.008$), and individuals with elevated ALT ($P = 0.034$) and AST serum levels ($P = 0.021$). Regarding HBV viral load, there was no significant difference between HBV/HDV co-infected and HBV mono-infected patients ($P = 0.07$).

Conclusions: Prevalence of HDV infection was found to be relatively high among HBsAg-positive cases in this region. Therefore, it is suggested to assess HDV antibodies among HBsAg-positive patients, especially those with higher serum levels of transaminases.

Keywords: Hepatitis D, Hepatitis B, Prevalence, Iran

1. Background

Hepatitis delta virus (HDV) is a small single-stranded defective human RNA virus. This virus depends on the presence of hepatitis B surface antigen (HBsAg) envelope proteins for its transmission and persistence (1). Approximately, 15 - 20 million people around the world are co-infected with hepatitis B virus (HBV) and HDV (2). When compared to the HBV mono-infection, HBV/HDV co-infection is associated with poor clinical outcomes, rapid progression to the cirrhosis, high risk of hepatocellular carcinoma and end-stage liver disease, and the high rate of mortality related to the liver disease (3). Transition modes are the same as the HBV infection although HDV is commonly transmitted via parenteral routes, demonstrating a remarkable threat to public health (4). Currently, there is no effective therapy for HDV infection (5).

The distribution of HDV infection varies around the

world with the highest prevalence rates in the Mediterranean Basin, the Middle East, central and northern Asia, sub-Saharan Africa, and South America (6). There are eight HDV genotypes scattered throughout the world. Genotype 1 is the most common genotype distributed in the Middle East, Europe, North America, and North Africa. Genotype 2 is endemic in the Far East, genotype 3 in South America, and genotypes 4 to 8 in Africa (6, 7). A reducing trend has been found in the epidemiology of HDV in the world including in countries with high endemicity. It could be due to the worldwide decreasing rate of HBV prevalence, HBV vaccination, and other preventive control measures (8, 9). However, migration and intravenous drug use can enhance HDV mono-infection (9).

Iran is an endemic area for hepatitis D with a prevalence of 14.4% in chronic HBV carriers, 30.47% in patients with cirrhosis, and 4.94% in inactive carriers (10, 11). HBV/HDV co-infection in the country differs widely from

zero in Sari, northern Iran, to 17.3% in Hamadan, western Iran (12, 13). Mashhad located in the northeast of Iran is a large city attracting many pilgrims from different parts of Iran and other countries. There are limited data about HDV infection frequency in this area (14).

2. Objectives

This study aimed to evaluate the prevalence of HDV infection and its association with HBV serological markers and liver transaminases among HBsAg-positive patients in Mashhad, northeastern Iran.

3. Methods

3.1. Study Population

This cross-sectional study was carried out on individuals admitted to the Central Diagnostic Lab of Academic Center for Education, Culture, and Research (ACECR), Razavi Khorasan Branch, Mashhad, Iran, from March 2017 to March 2018.

Based on the electronic database of the laboratory, anti-HDV antibody testing had been carried out for 606 HBsAg-seropositive individuals who referred to the laboratory during this period. The Research and Technology Deputy of ACECR, Razavi Khorasan Branch, approved the study for methodological and ethical issues (No.96.48.1745).

3.2. Laboratory Studies

The tests for serum HBsAg, hepatitis B e antigen (HBeAg), and antibody against HBeAg (anti-HBe) had been performed using commercial enzyme-linked immunosorbent assay (ELISA) kits (General Biologicals Corporation, Taiwan). Serum anti-HDV antibody tests had been also carried out via ELISA kits (DIA PRO Diagnostic Bioprobes, Srl, Italy). The serum concentration of alanine transaminase (ALT) and aspartate transaminase (AST) also had been assessed (Auto analyzer, Liasys, Germany). HBV viral DNA had been extracted from serum samples by the QIAamp DNA Blood Mini Kit (QIAGEN) and quantitative analysis of HBV DNA PCR had been performed using COBAS TaqMan HBV assay (Roche Diagnostics) according to the manufacturer's instruction.

3.3. Statistical Analysis

Statistical analysis was performed using SPSS version 19 software. Continuous variables are displayed as means \pm SD and categorical variables as frequencies and percentages. The chi-square test or Fisher's exact test were used

to compare statistical differences in the categorical variables between the groups. Independent sample *t*-test was used to compare the means of HBV viral load between the groups. The statistical significance level was considered at 5%.

4. Results

Among 606 HBsAg-positive individuals tested for the anti-HDV antibodies, 335 patients were male (55.3%) and 271 were female (44.7%). Participants' age ranged from 12 to 96 years with a mean of 43.6 ± 14.8 years. Serum samples of 35 subjects (5.8%) were positive for anti-HDV antibodies. As Table 1 shows, HDV infection was more prevalent among older subjects ($P = 0.008$). The frequency of elevated AST and ALT serum levels (> 40 mg/dL) were remarkably higher in HDV-positive cases than in HDV-negative cases ($P = 0.021$ and $P = 0.034$, respectively). There were no significant differences between two groups regarding patients' sex, the rates of HBeAg and Anti-HBe seropositivity and HBV viral load.

5. Discussion

Eastern Mediterranean basin and Middle East countries are endemic areas for HDV infection. Iran, as one of the countries located in the Middle East, shows a high prevalence of HDV infection, which differs from region to region (15). Therefore, estimating the prevalence of this viral infection in an area with a high prevalence seems necessary. This study demonstrated the HDV seropositivity rate of 5.8% among HBsAg positive patients who referred to ACECR lab in Mashhad.

Previous seroepidemiological studies showed different HDV seropositivity results among Iranian patients with no consistent pattern. The rate of HDV was reported to be zero in Mazandaran, 1.7% in Kermanshah, 2% in Qom, 2.9% in Isfahan, 5.8% in Golestan, 7.7% in Tehran, 11.5% in Khuzestan, 17% in Sistan and Baluchistan, and 17.3% in Hamadan provinces (9, 12, 13, 16-21). Amini et al. (11) in a systematic review of epidemiological studies reported the overall HDV seropositivity rate of 6.61% among Iranian patients with chronic HBV infection. Variations in HDV prevalence in different geographical areas in the country demonstrate that risk factors for HDV infection differ between the regions (16). Furthermore, discrepancies between different areas of the country in the severity of the disease among studied populations might be another reason for different frequencies of the infection. Amini et al. review (11) estimated that the HDV prevalence is considerably higher in cirrhotic patients (30.47%) than in those with chronic hepatitis (14.4%) and inactive carriers (4.94%). The findings of

Table 1. Characteristics of HBsAg-Positive Patients in HDV-Seropositive and HDV-Seronegative Groups^a

Variables	HDV Positive	HDV Negative	P Value
Age, y; mean \pm SD	59.03 \pm 16.39	43.23 \pm 14.67	0.008
Gender			0.201
Male	23/35 (65.7)	311/570 (54.6)	
Female	12/35 (34.3)	259/570 (45.4)	
Elevated serum SGOT	12/24 (50.0)	104/373 (27.9)	0.021
Elevated serum SGPT	12/24 (50.0)	111/377 (29.4)	0.034
HBeAg seropositivity	0/18 (0)	27/337 (8.0)	0.212
Anti-HBe seropositivity	9/11 (81.8)	219/271 (80.8)	0.198
HBV viral load, log₁₀, mean \pm SD	2.055 \pm 2.542	3.324 \pm 3.048	0.071

^aValues are expressed as No. (%) unless otherwise indicated.

the present study showed that the HDV infection prevalence is lower in Iran than in its neighboring countries. The HDV infection rate was reported to be as high as 14.66% among 1890 HBV patients from east and northwest of Pakistan (22). Likewise, the prevalence rates of the infection in Turkey (9.6%) and Iraq (6.6%) were higher than the prevalence reported in the present study (23, 24). Furthermore, an earlier study demonstrated a significantly higher HDV seroprevalence (26.66%) among Afghans who immigrated to Iran than among Iranian patients (1.85%) (25).

The current study in agreement with Tahaei et al. (19) and Sayad et al. (9) studies showed no significant relationship between gender and HDV seropositivity. However, some previous investigations demonstrated a greater seroprevalence for hepatitis D in men than in women due to the higher prevalence of risk behaviors among men (13, 21). On the other hand, in the present study, HDV seropositivity was more prevalent among older patients, which could be attributed to the reduced immunity, particularly compromised immune system in the elderly (26). Furthermore, in line with the results of Binh et al. (27) and Tahaei et al. (19) studies, the present study demonstrated higher levels of ALT and AST in HDV-seropositive patients probably due to that HDV infection intensifies liver inflammation (28).

Additionally, similar to the results of previous studies (3, 27), the present study showed higher levels of HBV DNA in HBV mono-infected patients than in co-infected patients; however, the difference was not statistically significant. Although HBV supplies envelope proteins and is crucial for HDV viremia and infectivity, HDV hinders HBV replication at a definite point of the coinfection due to the interference mechanisms that remain to be elucidated (29). In this study, there was no correlation between anti-HDV positivity and HBeAg/anti-HBe seroreactivity. Similarly, in a cross-sectional study by Ziaee and Azarkar (30) on chronic

hepatitis B patients, no association was found between positive anti-HDV serology and positive HBeAg serology.

5.1. Conclusions

In summary, hepatitis delta prevalence in Mashhad, northeast of Iran, was moderately high. HDV seropositivity was more prevalent among older people and those with higher ALT and AST levels. Considering the high prevalence of HDV in this area, screening of HDV antibodies is proposed in HBV patients, particularly those with elevated levels of ALT and AST.

Footnotes

Authors' Contribution: Mohammad Reza Hedayati-Moghaddam designed the study. Arman Mosavat, Sanaz Ahmadi Ghezeldasht, and Mohammad Mehdi Akbarin performed the assays and contributed to data interpretation. All authors wrote and reviewed the manuscript.

Conflict of Interests: It is not declared by the authors.

Ethical Approval: The study was approved by the Research and Technology Deputy of Academic Center for Education, Culture, and Research (ACECR), Razavi Khorasan Branch, Mashhad, Iran (IR.ACECR.JDM.REC.1397.3).

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