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Prevalence of Hepatitis D in HBsAg positive patients visiting liver clinics

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Abstract

Objective: To estimate the prevalence of hepatitis D in HBsAg (hepatitis B surface antigen) positive patients visiting liver clinics.

Methodology: All HbsAg positive patients who had visited two liver clinics; in Karachi and in Jacobabad, from October 2007 to March 2008, were included in this study. These patients were tested for HBV DNA and HDV RNA by PCR technique, HBeAg and anti-HDV. Clinical status of the patients was evaluated by examination, routine biochemical tests and ultrasound.

Results: Total numbers of patients included in the study were 362 comprising of 151 patients from the clinic in Jacobabad and 211 from Karachi. The patients ranged from 4 to 70 years age (mean age 29.75 ±11.27). Out of the total patients 297 (82%) were males. All the patients were screened for HDV antibody out of which 212 (58.6%) tested positive. Total 65 anti-HDV positive patients were tested for the HDV RNA by PCR, out of which 30 (46.2%) tested positive for the virus. Three hundred and forty (340) patients were screened for HBeAg, out of which 71 (20.9%) tested positive. Three hundred and seven patients were screened for HBV DNA by PCR, out of which 88 (28.7%) were positive for the virus. HBV DNA was positive in 16.2% of HbeAg negative patients (pre-core mutants). The frequency of positive HDV antibody was 69.23% in patients from Kashmir, 67% in Jacobabad, 65.4% in Jaffarabad, 65.21% in Quetta, 60% in Naseerabad, 36.58% in Karachi, 58.33% in other areas of Balochistan and 60.71% in other areas of Sindh. Positive HDV antibody status was associated with more severe and advanced disease (p<0.0001)

Conclusion: This data shows extremely high prevalence of hepatitis D in the referred patients from some areas of Southern Pakistan. Effective preventive measures are the need of the hour and Pakistan may be considered as one of the areas of highest HDV prevalence around the globe (JPMA 59:434; 2009).

Introduction

The hepatitis D virus (HDV) also known as hepatitis delta virus is a single stranded defective RNA virus consisting of 1679 nucleotides.¹⁻³ For its penetration into hepatocytes and assembly of virion it needs the help of hepatitis B virus (HBV) that provides the viral coat with the surface antigen.^{2,4,5} HDV can cause both rapid progression of already existing HBV Hepatitis and fulminant hepatitis.⁶

Infection by HDV can be caused either as a co-infection in individuals with HBV or as a superinfection in chronic HBV carriers.^{4,7,8} Individuals having HBV-HDV co-infection may have more severe acute disease and higher risk of fulminant hepatitis.^{6,7,9,10} Persons suffering from HDV superinfection have more risks of progressing rapidly to cirrhosis than the individuals suffering from HBV monoinfection.^{4,7,9,10} It is observed that most of individuals infected with HDV develops the chronic form of the disease and in approximately 80% of these individuals the chronic Hepatitis D progresses to cirrhosis within 5-10 years.¹ Another important feature of chronic hepatitis D is that it can give rise to hepatocellular carcinoma in the infected individuals.¹¹

Chronic hepatitis D treatment is presently unsatisfactory and the only agent which has some effect on the chronic infection is alpha interferon.^{2,7,8,10,12,13} Although HBV vaccine is useful in preventing both HBV and HDV,⁷ there is no effective measure to prevent HDV superinfection in HBV carriers.

HDV is an infection present worldwide and in all age groups but its distribution is not uniform and the general pattern of its distribution corresponds to that of the prevalence of chronic HBV infection.¹⁴ There are around 350 million carriers of HBV around the world and 18 million people have been infected with the virus.⁷ An important trend in the worldwide HDV infection is that a global decline in the prevalence of hepatitis D infection has been observed. This is true for both acute and chronic forms of the disease.⁸

Mumtaz et al noted a prevalence of 16.6% in HBsAg positive patients from different areas of Pakistan.¹⁵ The aim of this study was to estimate the prevalence of hepatitis D in hepatitis B surface antigen (HBsAg) positive patients visiting the liver clinics.

Methods

This study was conducted at two centres, Medicare Clinic in Karachi and Imam Clinic in Jacobabad. Along with the local residents, a significant number of patients from different parts of Sindh and Balochistan also visit these clinics for consultation.

The study included 362 HBsAg positive patients who visited these two liver clinics from October 2007 to March 2008. These were further screened for any activity of hepatitis B by hepatitis B e antigen (HBeAg) and HBV DNA by real time polymerase chain reaction (PCR). The patients were further screened for associated hepatitis C and D by doing antibody tests. These serological tests were performed on third generation ELISA AXSym Abbott (6.0) employing micro particle enzyme immunoassay. The patients who were anti-HDV positive were tested for HDV RNA by PCR. Other investigations that were ordered include complete blood count, serum alpha-fetoprotein, serum albumin and an ultrasound examination of the abdomen.

The clinical status of the patients was determined by examination, routine biochemical tests and ultrasound abdomen examination. Patients were divided into four categories namely (i) carrier of HBsAg (ii) active hepatitis (iii) compensated cirrhosis (iv) decompensated cirrhosis. The patients were labeled as clinically compensated cirrhosis on the basis of clinical and ultrasound findings suggestive of cirrhosis (nodular surface, firm consistency, blunt liver edge, altered echotexture, dilated portal vein and splenomegaly) and evidence of hypersplenism (platelets < 150 000/mm³). Decompensated cirrhosis was defined as presence of ascites, encephalopathy, variceal bleeding and hepatorenal syndrome. A standardized proforma was completed for each patient that includes age, sex, district of residence and clinical status of patient. All the data analysis was carried out using the SPSS software version 15.0.

Results

The total number of patients included in the study was 362 comprising of 151 patients from the clinic in Jacobabad and 211 from Karachi. The patients ranged from 4 to 70 years of age (mean age 29.75 ± 11.27) and 297 (82%) of the patients were male. Out of the total patients who visited these clinics, 97 (26.8%) were the residents of Jacobabad, 82 (22.7%) from

Karachi, 55 (15.2%) from Jaffarabad, 35 (9.7%) from Nasirabad, 26 (7.2%) from Kashmore, 23 (6.4%) from Quetta and remaining 44 (12.1%) from other parts of Sindh, Balochistan and Punjab.

All the patients were screened for HDV antibody, out of which 212 (58.6%) tested positive for the virus. Total 65 patients were screened for the HDV RNA by PCR out of which 30 (46.2%) tested positive for the virus.

Three hundred and forty (340) patients were screened for HBeAg out of which 71 (20.9%) tested positive for HBeAg. Three hundred and seven patients were screened for HBV DNA by PCR out of which 88 (28.7%) tested positive for the virus. Out of 269 patients that tested negative for the HBeAg, 229 were screened for HBV DNA by PCR of which 37 (16.2%) tested positive for the HBV DNA by PCR and represented the pre-core mutant form of the disease. Out of the 71 patients who tested positive for HBeAg, 61 were screened for HBV DNA by PCR out, of which 48 (78.7%) tested positive.

The prevalence of the HDV antibody was 69.23% in Kashmore, 67% in Jacobabad, 65.4% in Jaffarabad, 65.21% in Quetta, 60% in Nasirabad, 36.58% in Karachi, 58.33% in other areas of Balochistan and 60.71% in other areas of Sindh as shown in Table-1.

Table-1: Prevalence of HDV patients visiting clinics from different areas.

Area	HDV Ab +ve Patients	Total Patients	Percentage
Jacobabad	65	97	67%
Karachi	30	82	36.58%
Jafferabad	36	55	65.4%
Naseerabad	21	35	60%
Kashmore	18	26	69.23%
Quetta	15	23	65.21%
Other Areas of Sindh	17	28	60.71%
Other Areas of Balochistan	7	12	58.33%
Southern Punjab	3	4	75%

One hundred and sixteen (116) of the total patients were screened for the hepatitis C virus antibody (HCV Ab) out of which 18 (15.5%) tested positive.

Of the total patients visiting the clinics, 284 (78.5%) were clinically non-cirrhotic and 78 (21.5%) were cirrhotic

Table-2: Effect of HDV antibody status on disease severity.

Clinical Status	Total Patients	HDV Ab Positive	HDV Ab Negative	p-value*
Carrier of HBV	143	53	90	<0.0001
Active Hepatitis B	141	95	46	<0.0001
Compensated Cirrhosis	34	29	5	<0.0001
Decompensated Cirrhosis	44	35	9	<0.0001

* p-values by Pearson Chi-Square Test.

comprising of 44 (12.2%) patients with decompensated cirrhosis and 34 (9.4%) with compensated cirrhosis. Positive HDV antibody status was associated with more severe and advanced disease ($p < 0.0001$) (Table-2 & Figure).

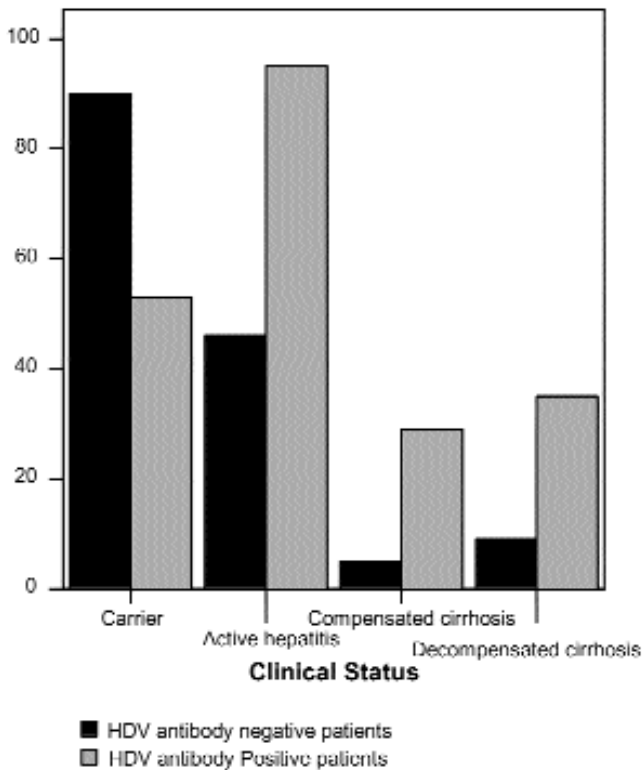


Figure: Bar Chart comparing clinical status of HDV antibody positive and negative patients.

Discussion

This study shows an extremely high prevalence of HDV infection in some pockets of Southern Pakistan. The majority of the high prevalence areas come from rural areas of Sindh and Balochistan. However, HDV prevalence is even not low in urban cities like Karachi and Quetta, as indicated by our results. Although the sample size that showed these results is not too large as the patients included in the study are those who visited the liver clinic. However, this study provides a new data from places like Kashmore, Jacobabad, Jaffarabad and Naseerabad which are highly HDV prevalent and were not previously documented in any epidemiological survey. In the light of current available data these areas can be regarded as the regions with highest prevalence of HDV infection in Pakistan. Figure 1 and table 2 shows the comparison of the clinical status of HDV positive and negative patients.

We observed higher HDV prevalence in young males. This is in corroboration with the findings of a previously done epidemiological survey in Pakistan.¹⁵ This could be due to the higher frequency of injectible drug abuse and the use of

contaminated needles for therapeutic injections.¹⁶ Sexual transmission is another possible explanation for this high prevalence.¹⁵

In Pakistan according to an epidemiological survey that included 8721 HBV patients over 14 years of age and tested for anti-HDV antibody from all over the country, the HDV prevalence was 16.6%. The study added that a large belt of rural area exists in the middle of the country with a high prevalence of HDV.¹⁵ Our study showed an overall prevalence of 58.6% which is much higher than the 7 year old data. However, this may be because the patients of this study were from areas of higher prevalence and also visiting a specific clinic which may not reflect the true disease prevalence.

As mentioned before, an overall decline in the worldwide HDV infection has been observed.⁸ This decreasing trend is the result of global vaccination and hence HDV infection is expected to be decrease with time.¹⁷⁻¹⁹ Research results in India have shown a decline in HDV infection similar to the trend seen world wide.¹⁸ The same trend is also observed in Turkey.¹⁹ However, in a developing country like Pakistan due to lack of resources and therefore lack of preventive strategies, HDV prevalence seems to be on the rise.

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