MEDICAL CHANNEL

Original Article

HEPATITIS DELTA VIRUS CAUSING FULMINANT HEPATIC FAILURE MORE FREQUENTLY THAN OTHER LIVER DISEASES

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ABSTRACT:

Objective: To study the prevalence and effect of HDV infection in Hbs Ag positive patients

Introduction: The cases of HDV infection are declining worldwide, but in Pakistan there is an increase in prevalence. Hbs Ag positive patients may be infected with HDV as co infection or super infection. The liver disease becomes severe and chances of development of acute Fulminant hepatitis increase. There was need to see the effect of HDV in Hbs Ag positive patients regarding liver damage. Therefore the study was designed to see the prevalence and effect of HDV.

Material And Method: This is descriptive cross sectional study which was done in two hospitals of Karachi from January 2010 till December 2011. All Hbs Ag positive patients were included. The patients with HCV, HAV, HEV, alcoholic, metabolic, drug induced and autoimmune hepatitis were excluded. All patients went through anti HDV antibody detection test and a series of tests to determine co infection, super infection, acute fulminant hepatitis, hepatocellular carcinoma, acute hepatitis and cirrhosis.

Result: In total 310 patients, the anti HDV positive patients were 24.51% (n=76). There were 65.2% male (n=202) and 34.8% (n=108) female. The co infection with HDV was 5.25% (n=17) while super infection 19.1% (n=59) with significant difference (p-value=0.002). The acute hepatitis was 25.16% (n=78), HCC was 7.4% (n=23), cirrhosis of liver 39.35% (n=122) and there was no significant difference between HDV seropositive and HDV seronegative groups. The acute Fulminant hepatitis was 4.8% (n=15) which was significantly associated with HDV seropositive group (p value =<0.001).

Conclusion: Acute fulminant hepatic failure was more commonly associated with HDV seropositive group than cirrhosis, acute hepatitis and HCC.

KEYWORDS: HDV, Acute Fulminant Hepatitis

INTRODUCTION

HDV was described by Rizzetto in 1977.[1] The Delta virus is an incomplete RNA virus which depends on HBV for its replication.[2] The HDV causes acute and chronic hepatitis with hepatitis B[3,4] which may occur as co infection or super infection.[5] The chronic hepatitis by HDV usually develops with super infection.[3] The clinical studies have reported that patient with chronic infection of HBV and HDV revealed more severe liver disease than HBV alone.[6] The risk of CLD and HCC was reported to increase up to 3 fold.[7] The individuals having co infection may develop more severe acute hepatitis and chance of fulminant hepatic failure increase.[8,9] The reported risk is 10 fold for acute fulminant hepatic failure.[7] The prevalence of HDV reported in some studies is over 15 million especially in Italy, Eastern Europe, Asia and middle East.[10] The studies from Pakistan give different prevalence in different regions. The study by

Mumtaz and colleague[10] reported 16.6%, Seetlani et al[11] reported 58.6%, and Zaidi[12] reported 88.8%, while zuberi[13] described the prevalence ranges between 16-27% in review article. The HDV prevalence is decreasing worldwide.[14, 15] The reason for decreasing prevalence of HDV is decrease in prevalence of HBV due to vaccination, [11, 15, 16] but in Pakistan HDV infection is increasing. Therefore, to figure out the prevalence of HDV and its effect on liver disease, the study was conducted in the targeted population presented to two tertiary care hospitals of Karachi.

MATERIAL AND METHOD

This is a descriptive cross sectional study which was conducted in Sindh Govt. Lyari General Hospital Karachi and Civil Hospital Karachi for duration of 2 years from January 2010 till December 2011. The data was collected from medical wards, OPD and liver clinics. All Hbs Ag positive patients were included and underwent for anti HAV IgM, anti HCV and anti HEV IgM. The patients with HAV IgM positive, antiHCV positive and anti HEV IgM positive were excluded from the study. The patients with suspicion of metabolic liver disease, autoimmune hepatitis, alcoholic and drug induced liver disease were excluded. The anti HDV antibodies were performed in all patients but due to financial constrain HDV PCR was not done. The patients were divided in to two groups anti HDV seropositive and anti HDV seronegative on the basis of anti HDV presence. All patients underwent a list of investigations including HBe Ag, Anti HBc IgM, and HBV PCR, CBC, LFTs, PT, Albumin, Urea, Creatinine, Ultrasound abdomen, Serum ammonia, Liver biopsy and Endoscopy. The patients with HBc IgM with anti HDV positive were considered co infection. The patients with HBc IgM with anti HDV negative were considered as acute HBV infection without HDV infection. The patients with HBe Ag positive and HBV PCR positive were considered in acute replication of hepatitis B virus and if they are positive for anti HDV, considered as super infection. The patients with HBe Ag negative and HBV PCR positive were considered as pre core mutant and if they are positive for anti HDV considered as super infection. The patients who were only Hbs Ag positive without any other positive antibodies were considered as carrier. The liver disease was divided in four groups, acute hepatitis, acute fulminant hepatic failure, and cirrhosis and HCC. The data was analyzed by SPSS 17 and chi square was applied considering p value <0.05 as significant.

RESULTS

In total 310 patients, 65.20% (n=202) were males and 34.80% (n=108) females with statistically significant p value (0.004). There were total 24.51% (n=76) hepatitis D positive cases. The cases of co infection were 5.45% (n=17) while cases of super infection were 19.1% (n=59) which was significantly higher (p-value=0.002). The commonest age group was 16-34 years (55.5%) with no significant difference in HDV positive and HDV negative. Most of our patients were from rural Sindh (38.7%) and Baluchistan (30.64%). The Lyari town had more cases (19.7%) than other areas of Karachi (10.96%) with no significant difference (p-value = 0.565) between anti HDV positive and anti HDV negative. Regarding liver damage by HDV like acute hepatitis, HCC and

TABLE 1
DEMOGRAPHIC DATA

Categories	Variables	Anti HDV +ve	Anti HDV -ve	Total	df	p –value chi square	p-value fisher exact
Gender	Male Female	60 (19.4%) 16 (5.2%)	142 (46%) 92 (30%)	202 (65.2%) 108 (34.8%)	1	0.004	0.004
Age	16-34 years 35-55 ears > 55 years	41 (13.2%) 26 (8.4%) 09 (3%)	131 (42.3%) 81 (26%) 22 (7%)	172 (55.5%) 107 (34.5%) 31 (10%)	2	0.824	—
Residence	Karachi Lyari town Sindh Baluchistan	10 (3.23%) 16 (5.16%) 28 (9.1) 22 (7.1%)	24 (7.7%) 45 (14.5%) 92 (29.7%) 73 (23.5%)	34 (10.1%) 61 (19.7%) 120 (38.7%) 95 (30.6%)	3	0.868	—
HBc IgM	Positive Negative	17 (5.45%) 59 (19.03%)	21 (6.77%) 213 (68.71%)	38 (12.3) 272 (87.7%)	1	0.002	0.004
HBe Ag*	Positive Negative	42 (13.59%) 34 (11%)	86 (27.8%) 147 (47.57%)	128 (41.4%) 181 (58.6%)	1	0.005	0.007
HBV PCR	Positive Negative	76 (24.51%) 00	150 84 (27.1%) (48.38%)	226 (72.9%) 84 (27.1%)	1	<0.0001	<0.0001

***number of cases 309**

TABLE 2
LIVER DISEASES

Categories	Variables	Anti HDV +ve	Anti HDV -ve	Total	df	p –value chi square	p-value fisher exact
Acute Hepatitis	Positive Negative	23(7.4%) 53(17.1%)	55 (17.74%) 179 (57.7%)	78 (25.2%) 232 (74.8%)	1	0.238	0.287
Hepatocellular carcinoma	Positive Negative	09 (2.9%) 67 (21.6%)	14 (4.5%) 220 (71%)	23 (7.4%) 287 (92.6%)	1	0.090	0.127
Acute fulminant hepatic failure	Positive Negative	10 (3.2%) 66 (4.8%)	05 (1.6%) 229 (73.9%)	15 (4.8%) 295 (95.2%)	1	<0.001	<0.001
Cirrhosis of liver	Positive Negative	36 (11.6%) 40 (12.9%)	86 (27.7%) 148 (47.7%)	122 (39.3%) 188 (60.7%)	1	<0.001	0.107
Carrier stage	Carrier Not carrier	00 76 (24.6%)	83 (26.8%) 151 (48.6%)	83 (26.8%) 227 (73.2%)	1	<0.001	<0.001
ChildPugh Classification of Cirrhosis	Class A Class B Class C Not cirrhotic	24 (7.7%) 06 (1.9%) 06 (1.9%) 40 12.9%)	56 (18.1%) 20 (6.45%) 11 (3.5%) 147 (47.4%)	80 (25.8%) 26 (8.4%) 17 (5.5%) 187 (60.3%)	3	0.336	—

TABLE 3
COMPLICATIONS OF LIVER DISEASES

Categories	Variables	Anti HDV +ve	Anti HDV -ve	Total	df	p –value chi square	p-value fisher exact
Ascites	Present Absent	13 (4.2%) 63(20.3%)	21(6.8%) 213(68.7%)	34 (11%) 276 (89%)	1	0.343	
SBP	Present Absent	05 (1.6%) 71 (22.9%)	08 (2.5%) 226 (72.9%)	13 (4.1%) 297 (95.9%)	1	0.232	0.319
Encephalopathy	Grade 1 Grade 2 Grade 3 Grade 4 No encephalopathy	03 (1%) 05 (1.6%) 03 (1%) 13 (4.2%) 52 (16.8%)	04 (1.3%) 15 (4.8%) 04(1.3%) 09 (2.9%) 202 (65.2%)	07 (2.3%) 20 (1.4%) 07 (2.2%) 22 (7.1%) 254 (82%)	4	0.001	—
Hepatorenal syndrome	Type I Type II No hepatorenal syndrome	02 (0.7%) 02 (0.7%) 72 (23.2%)	00 02 (0.7%) 232 (74.8%)	02 (0.7%) 04 (1.2%) 232 (98.1%)	2	0.022	—
Anemia	Present absent	36 (11.7%) 40 (13.1%)	38 (12.4%) 193 (62.9%)	74 (24.1%) 233 ((75.9%)	1	<0.001	<0.001
Upper GI bleeding	Present Absent	16 (5.2%) 60 (19.5%)	09 (2.9%) 222 (72.3%)282	25 (8.1%) (91.9%)	1	<0.001	<0.001

TABLE 4
LABORATORY FINDING IN LIVER DISEASES

ategories	Variables	Anti HDV +ve	Anti HDV -ve	Total	df	p –value chi square
S.Albumin *	Less than 2.8 g/dl 2.8-3.5 g/dl	08(2.6%) 15 (4.8%) 51 (16.61%)	07 (2.28%) 24 (7.8%) 202 (65.79%)	15 (4.8%) 39 (12.6%) 253 (81.2%)	2	0.001
Prothrombin time	1-3 seconds 4-6 seconds More than 6 seconds	48 (15.5%) 11 (3.5%) 17 (5.5%)	194 (62.6%) 17 (5.5%) 23 (7.4%)	242 (78.1%) 28 (9%) 40 (12.9%)	2	0.001
SGPT	Normal 2 times 5 times More than 5 times	33 (10.6%) 12 (3.9%) 08 (2.6%) 23 (7.4%)	172 (55.5%) 07 (2.3%) 20 (6.4%) 35 (11.3%)	205 (66.1%) 19 (6.1%) 28 (9%) 58 (18.7%)	3	<0.001
S. Billirubin	Less than 2 mg/dl 2-3 mg/dl More than 3mg/d	32 (10.3%) 10 (3.2%) 34 (10.9%)	166 (53.5%) 29 (9.4%) 39 (12.6%)	198 (63.8%) l39 (12.6%) 73 (23.5%)	2	<0.001

*number of cases 307

cirrhosis there was no significant difference between HDV seropositive and HDV seronegative groups. The cases of fulminant hepatic failure were 4.8% (n=15) in which 3.2% (n=10) were HDV positive so there was significant difference between two groups (p-value<0.001).

There was significant difference between HDV positive and HDV negative cases regarding hepatic encephalopathy, hepatorenal syndrome, anemia and upper GI bleeding (p-value < 0.001).

The total 4.8% (n=15) cases had albumin less than 2.8g/dl in which 2.6% (n=8) cases were HDV positive. The serum albumin was significantly lower in HDV positive patients (p-value = 0.001).

The prothrombin time was more than 6 seconds in 12.9% (n=40) cases in which 5.5% (n=17) cases were HDV positive. The prothrombin time is significantly elevated in HDV positive group (p-value=0.001). There was significant difference between HDV positive and HDV negative groups regarding SGPT and serum billirubin (p-value=<0.001).

DISCUSSION

The prevalence of HDV in Hbs Ag positive patients revealed 24.51% in our study which is in the range of prevalence shown in a review article (16-27%)[13], but it is in contrast to the study done by Seetlani (58.6%)[11] and Zaidi (88.8%)[12]. In our study super infection (19.01%) showed high prevalence which is in contrast with co infection (5.45%). Therefore only few patients had infection with same source and most of the patients got super infection on pre existing liver disease. These finding are similar to study done by Zuberi[17]. The patients with super infection usually develop cirrhosis, chronic hepatitis and hepatocellular carcinoma while patients with co infection had acute hepatitis and acute fulminant hepatic failure.

The most of the patient with HDV infection were young male in the study done by Khan[18] and the same finding was revealed in our study that 90% of the patients were from age group less than 55 years. There was significantly difference between male (65.2%) and female (34.8%) patients (p-value = 0.004). This finding may be due to more presentation of male gender to these two hospitals especially from Interior Sindh and Baluchistan. The study by Khan[18] explains more prevalence in Sindhi population compare to Punjabi and Pashtoon population which is in contrast to Zaidi[12] which revealed 88.8% prevalence in Punjab. Another study by Aziz[19] describes that most of the patients are from rural Sindh. In our study the most of the patients were from rural Sindh (38.7%) but there was no statistically significant difference was found in HDV seropositive and HDV seronegative groups regarding area of residence (p-value = 0.565).

The most important finding in our study was the development of acute fulminant hepatic failure which was significantly higher as seen in our patients with HDV positive (p-value < 0.001) which is similar to the study by Fattovich[7] which explains 10 times greater risk of Fulminant hepatic failure with HDV infectivity. The complications like ascites and spontaneous bacterial peritonitis were not significantly different in HDV positive and HDV negative groups which is similar to the previous study.[17] The hepatic encephalopathy, hepatorenal syndrome , anemia and upper GI bleeding were significantly associated with HDV seropositive group (p-value <0.001). The laboratory finding also revealed that more abnormalities were found in HDV seropositive group. So SGPT was significantly raised more than five times, billirubin was more than 3mg/dl, serum albumin was less than 2.8g/dl and

prothrombin time was more than 6 seconds in HDV positive patients (p-value <0.001).These findings explain that HDV is associated with more damage to the liver and causing more complications with existing hepatitis B infection which also similar to the previous study.[17]

The only treatment available for HDV positive patients is pegylated interferon[20,21] which is very costly for poor socioeconomic group, so the most important step can be taken is prevention. As HDV cannot survive without hepatitis B virus so the consideration of prevention of HBV should be done by vaccination. There was a decline of HDV infection world over14 which may be due to vaccination against HBV. But in Pakistan the prevalence is still high because in rural areas the vaccination against HBV is not as much familiarize as in urban areas. The study is also showing that most of the patients were from rural areas of Sindh and Baluchistan and Lyari town which is an underdeveloped part of Karachi where awareness of vaccination is poor. Therefore, to prevent HDV infection we have to organize the vaccination program against hepatitis B virus, especially for adult population.

The limitation of our study is that the numbers of the patients were only 310 and the population was taken only from two tertiary care hospitals of Karachi where most of the patients are from rural Sindh and Baluchistan. This may not be true representation of the target population of whole Pakistan. Another limitation of the study is that there was no facility available to do PCR for HDV, which may show the activity and need of treatment for HDV infection.

CONCLUSION:

The HDV infection is causing more complications and damage to the liver in Hbs Ag positive patients. Therefore all patients who are Hbs Ag positive should go for anti HDV test. The another recommendation by the study is that as much as we will widen the spectrum of vaccination against hepatitis B virus we can prevent not only HBV infection but also HDV infection.

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