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ORIGINAL ARTICLE

Hepatitis D seroprevalence: An alarming situation and war without weapon.

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ABSTRACT… Objective: To determine the seroprevalence of HDV in HBs Ag positive patients and the burden of true viral hepatitis infection (viremia) as evidenced by detectable either HBV DNA and/or HDV RNA (single or dual infection). **Study Design:** Cross-sectional Observational Study. **Setting:** Al-Tibri Medical College Hospital, Karachi, and OPD Saylani Welfare Trust, Karachi. **Period:** August 2021 to July 2022. **Material & Methods:** All patients of both genders with HBsAg positivity were included in the study. All included subjects underwent a process of evaluation through history, physical examination, baseline or specific laboratory tests of Anti HDV Ab and PCR for detection of HBV DNA and HDV RNA, if applicable, followed by classification of subjects as follows: group I: Only HBs Ag positive (no active infection), group II: HBs Ag positive along with HBV DNA detected by PCR (HBV infection), group III: HBs Ag and Anti HDV Ab positive but no HBV or HDV viremia (no active infection), group IV: Both HBs Ag and Anti HDV Ab positive with HBV viremia (HBV infection), group V: Both HBs Ag and Anti HDV Ab are positive for HDV viremia (HDV infection), and group VI: Both HBs Ag and Anti HDV Ab positive with both HBV and HDV viremia (Dual infection). **Results:** A total of 237 subject's data were analyzed with a mean age of 29.03±9.262 years (range of 12 to 66 years), with males 143 (60.3%) and females 94 (39.7%), but dual infection was more prevalent in females, but statistically these differences turned out to be insignificant (p-0.061). According to age group, almost 89.5% of subjects were below the age of 40, while only 10.5 % were >40 years of age. Another significant finding in our results was that all 11 subjects in group VI (with dual viral infection) were under the age of 40 years. and this difference was statistically significant too (p 0.001), as shown in Table I. **Conclusion:** Our study highlighted that HDV is still prevalent in our part of the world and that it mainly affects younger age groups. Hence, it demands an urgent, extensive screening campaign of the masses to assess the exact HDV burden and offer preventive measures, including a vaccine against HBV. Otherwise, due to deficient treatment options, we have to lose the battle because this is the war and we are without weapons.

Key words: Hepatitis D, HDV, PCR, RNA, Seroprevalence.

INTRODUCTION

Hepatitis D virus (HDV), originally an animal virus first detected by Rizzetto et al.[1] in 1977, requires the support of hepatitis B virus (HBV) to infect humans. Chen et al. recently estimated that over 60 million people have been exposed to HDV, even though the precise worldwide HDV infection burden is not fully established.[2] HDV can cause a wide range of clinical symptoms, like acute infection, which usually occurs after simultaneous accretion of HDV and HBV or via HDV superinfection of HBsAg carriers. HDV can lead to chronic infection in almost 90% of cases of superinfection in HBs Ag carriers.[3,4] The advancement of cirrhosis, hepatocellular carcinoma, end-stage liver disease, and death are all accelerated by HBV/HDV coinfection compared to HBV alone infection.[4-6] With a rapid progression to cirrhosis, a higher risk of decompensation, and a higher mortality rate, chronic hepatitis D (CHD) is regarded to be the most severe form of chronic viral hepatitis.[7] In reality, 5 years after infection, 10-15% of patients with persistent infections may develop cirrhosis, and by 30 years later, this figure may reach 80%.[5]

The epidemiology of HDV has been changing in the last few decades, mainly due to the arrival of HBV vaccination, and the counties that added this prophylactic measure to their national

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immunization program have reported a decline in HDV cases. Furthermore, because vaccination campaigns against HBV were initiated in high-income nations in the 1990s, the younger generations are automatically protected from HDV as well as HBV.[8,9] However, hotspots have been noted in Vietnam[10] Yakutia[11], and Pakistan, where HDV infection remained a serious medical problem[12], with 30 to 50 % of HBsAg positive patients concentrated in a well-defined region in the centre of the country known as the "Delta Belt." In Pakistan, HDV/HBV co-infection has been underestimated and is very high among the population, with HDV-1 being the most prevalent HDV genotype.[13] According to a 2009 study, the prevalence of anti-HDV antibodies in the Pakistani population was 58.6%.[14]

The identification of anti-HDV antibodies by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA) is the basis for the diagnosis of hepatitis D and is presently regarded as a first-line screening method for HDV infection detection. By using reverse transcription polymerase chain reaction (RT-PCR) to identify HDV RNA, it is possible to confirm an active infection. This method, together with the presence of a positive anti-HDV antibody, aids in the differentiation of active infections from chronic and past infections and the tracking of therapeutic responses.[15]

The most challenging aspect of HDV infection is its treatment; as yet, there is no specific direct-acting antiviral treatment; hence, to date, recommendations for treatment of CHD are confined to a lengthened therapy of pegylated interferon-alpha. Keeping in mind all these challenging aspects of HDV infection, we planned to carry out a study on the actual burden of active HDV infection and its relation to HBs Ag as well as anti HDV antibodies in Pakistan.

MATERIAL & METHODS

This cross-sectional study was carried out at the department of Medicine at Al Tibri Medical College and Hospital Karachi and the Hepatitis OPD at Saylani Welfare Trust Karachi from August 2021 to July 2022. All patients of either gender who presented to the Outpatient Department or were hospitalized and found to have HBsAg were included in the study. The exclusion of subjects from the study was based on suspicion or evidence of non-viral hepatitis or a previous history of treatment against any of those viral hepatitis.

All those subjects who satisfied the inclusion criteria underwent a thorough process of detailed medical history, physical examination, investigations (complete blood count, liver function test, ultrasonography), as well as a set of specific laboratory tests like anti-HDV Ab, polymerase chain reaction (PCR) for detection of HBV DNA and HDV RNA, and in case it turned out to be positive, then PCR for detection of HDV RNA (quantitative/viral load to assess active viral replication, infection, or disease status) and divided as follows:

Group I: Only HBs Ag positive (no active infection)
Group II: HBs Ag positive along with HBV DNA detected by PCR (HBV infection)
Group III: HBs Ag and Anti HDV Ab positive but no HBV or HDV viremia (no active infection)
Group IV: Both HBs Ag and Anti HDV Ab positive with HBV viremia (HBV infection)
Group V: Both HBs Ag and Anti HDV Ab are positive for HDV viremia (HDV infection).
Group VI: Both HBs Ag and Anti HDV Ab positive with both HBV and HDV viremia (Dual infection).

An informed consent from each participant was obtained, and ethical approval was also obtained before initiating the study (IERC/ATMC/2021/73).

Data Analysis

Study Data were analyzed using SPSS 23 (Statistical Package for Scientific Studies version 23). Data were described as mean and standard deviation (SD), while comparisons between different qualitative variables were done using the Chi-Square test. A p-value of less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 237 subjects satisfied the inclusion criteria, and their data were analyzed with a mean age of 29.03±9.262 years (range of 12 to 66 years). Among those predominant were males,

143 (60.3%), while 94 (39.7%) were females, although dual infection was more prevalent in females. However, statistically, these differences turned out to be insignificant (p 0.061). According to age group, majority (89.5%) of subjects were ≤40 years of age and only 10.5 % of study subjects belonged to middle or older age (>40 years). Another significant finding in our study results was 11 subjects were presented in group VI (with dual viral infection) and all belonged to the age of ≤40 years (07 were in the 20-year group and 04 were in the age group of 20–40 years), and this difference was statistically significant too (p 0.001), as shown in Table-I.

Risk factors for acquiring viral hepatitis infection were found in more than 50% (121 subjects) of the study population. Among well recognized risk factors, the two most frequent risk factors were history of a local practitioner for injections or syringes was positive in 44 (18.6%) subjects; and a barber's visit was found in 36 (15.2%) subjects, as shown in Table-I.

There are statistically significant differences in the history of encephalopathy among different groups present, which were considered statistically significant with a p value of 0.04. However, no significant p-value was found when comparing the groups in regards to hematemesis, malena, and evidence of chronic liver disease as detected by ultrasound.

Laboratory parameters among these different groups of subjects were also analyzed. The 43(18.1%) subjects were anemic, 23 (9.7%) subjects had leukopenia (<4.0), while 82 (34.6%) had leukocytosis. Similarly, thrombocytopenia was present in 48 (20.3%). All those findings on laboratory parameters turned out to be statistically insignificant, as shown in Table-I. Only 6 (2.5%) of the subjects had normal ALT levels, while the rest of the 231 (97.5%) had abnormal ALT levels. Only 10 out of 11 subjects had raised ALT with 04 subjects had very high (5 times upper normal levels) ALT of >200. Hence the ALT had no significant relation with different groups.

DISCUSSION

Widely variable seroprevalence of viral hepatitis, especially HDV, from different studies in the same region has been under discussion among researchers. In recent years, advances in the treatment of viral hepatitis have proven a higher treatment response with fewer adverse effects related to treatment, but hepatitis D treatment has exactly the opposite pattern of a lower treatment response with higher adverse effects and has still remained a big challenge for any health care system in the World. Hence, chronic hepatitis D is recognized as the most severe form of viral liver disorder.[16] Moreover, the unknown exact prevalence of HDV and younger population involvement highlight the need for a robust weapon to fight the war against HDV.

In our study, we found 49.8% of HBsAg patients have anti HDV Ab seroprevalence, and our findings are comparable with those of a study by Mumtaz et al.[12] who found 30–50% of HBsAg positive patients were seropositive in a large but well defined area in the middle of the country, so called the "Delta belt," but another study by Abbasi et al.[17] reported a bit lower prevalence of 28.1%. This variability could be due to differences in geographical patterns of study population selection, as reported in the literature. Overall, a marker of true HDV infection as evidenced by HDV RNA detectability by PCR was present in 29.7% of cases, which was consistent with the study by Khan et al[18] who reported the HDV RNA positivity rate was 28% in 2011 in HBV viremic patients. More alarming finding among those 35 (29.7%) patients, 11 have coinfection of HBV as evidenced that they had HBV DNA was also detected. The most disquieting finding in the current study was that the majority of younger groups of the study population were affected by both anti HDV seroprevalence and viremia. These age related findings were in agreement with a study by Abbas et al[19], where they conducted a study in Pakistan and found the median age of HDV patients to be 22 years, while on average they were 32.7 years old. Undoubtedly, a large number of additional research conducted in Pakistan have revealed that patients with hepatitis D were primarily young adults (aged 21 to 40).[18,20]

Variable	Group I n-77	Group II n-41	Group III n=36	Group IV n=47	Group V n=25	Group VI n=11	P-Value
Age (Years)							
<20 27	01	06	03	07	03	07	
20-40 185	67	27	31	36	20	04	0.001
41-60 20	08	06	02	02	02	00	
>60 05	01	02	00	02	00	00	
Gender							
Male 143	45	17	26	33	16	06	0.061
Female 94	32	24	10	14	09	05	
Tribe/Race							
Baloch 07	02	01	02	00	02	00	
Pathan 39	12	06	09	07	04	01	
Punjabi 38	19	07	05	03	02	02	0.209
Sindhi 49	10	12	06	11	06	04	
Urdu 96	29	15	13	24	11	04	
Others 08	05	00	01	02	00	00	
Risk Factor							
Blood transfusion							
Yes 30	08	05	04	05	04	04	
No 207	69	36	32	42	21	07	
Barber visits							
Yes 36	10	04	10	03	07	02	
No 201	67	37	26	44	18	09	0.311
Tattoo marks							
Yes 11	03	04	00	03	01	00	
No 226	74	37	36	44	24	11	
Syringes Reuse							
Yes 44	14	07	06	11	03	03	
No 193	63	34	30	36	22	08	
Ultrasonography							
Shrunken liver							
Yes 11	01	00	04	04	02	00	
No 226	76	41	32	43	23	11	
Ascites							
Yes 13	02	01	05	03	02	00	
No 224	75	40	31	44	23	11	0.950
Dilated portal vein							
Yes 14	03	01	04	04	01	01	
No 223	74	40	32	43	24	10	
Splenomegaly							
Yes 16	01	02	06	04	03	00	
No 221	76	39	30	43	22	11	
H/O Encephalopathy							
Yes 02	00	00	02	00	00	00	0.046
No 235	77	41	34	47	25	11	
H/O Hematemesis/Malena							
Yes 10	01	03	02	01	02	01	0.441
No 227	76	38	34	46	23	10	
Hemoglobin (gm/dl)							
< 10 43	14	08	05	10	06	00	0.576
≥ 10 194	63	33	31	37	19	11	
WBC							
< 4.0 23	11	05	03	02	01	01	0.539
4-11 132	45	22	18	26	13	08	
>11 82	21	14	15	19	11	02	
Platelet Count							
< 150 48	13	07	08	13	06	01	0.616
≥ 150 189	64	34	28	34	19	10	
ALT (IU/L)							
<40 06	01	02	01	01	00	01	
40-80 103	44	18	15	15	11	00	
81-120 46	15	11	06	08	04	02	0.195
121-160 26	05	02	05	06	05	03	
161-200 13	03	02	02	04	01	01	
>200 43	09	06	07	13	04	04	

Table-I. Demographic, Clinical and laboratory characteristics of study subjects

But this is in contrast to the findings from Romania, a country in Eastern Europe where HDV infection still has a high morbidity rate, where the infection rate has decreased and the majority of patients are over 50.[21] This discrepancy might be multifactorial, like differences in race, geography, the status of the health care system, and national surveillance services.

Diversification of recommendations by the major societies currently engenders a main hindrance to a universal and uniform screening approach for HDV diagnosis, like guidelines from Europe suggesting screening for HDV in all HBV-infected patients[22], while the approach in the United States is screening for HDV confined only to patients having specific risk factors (immigrants of high HDV endemicity, individuals with IV drug users or high-risk sexual behavior histories, people with HCV or HIV infection, and patients with raised liver enzymes with decreased or undetectable HBV DNA)[23], despite the fact of increasing evidence suggestive of a suboptimal HDV infection diagnosis.[24,25]

In our assessment, the main factor contributing to this underestimation of true HDV prevalence is the lack of consensus on extensive testing for HDV in HBsAg positive individuals, which should be widely recommended or available. As we are all aware of flaws and limitations in treatment options with low response rates, higher adverse effects, and even higher relapse rates in responders, the only available solution to this problem is vaccination for HBV and avoidance of risk factors; otherwise, we have to lose because this is the war without a vigorous weapon.

LIMITATION

There was main limitation of this study; firstly, only Karachi based study with limited sample hence results cannot be generalized.

CONCLUSION

This study has highlighted that HDV is still prevalent in our part of the world and mainly affects younger age groups. Hence, it is highly recommended to launch an extensive screening campaign on a larger national level to assess the exact HDV burden and offer preventive measures, including a vaccine against HBV. Otherwise, due to deficient treatment options, we have to lose the battle because this is the war and we are without vigorous weapons.

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