Cross-sectional Study

ANNALS OF MEDICINE & SURGERY

OPEN

Prevalence and clinical characterization of hepatitis D virus (HDV) infection among Sudanese patients with hepatitis B virus (HBV): a cross-sectional study

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Background: Sudan has a high prevalence of hepatitis B surface antigen, exceeding 8%. The prevalence of hepatitis B varies across different regions of Sudan, ranging from 6.8% in central Sudan to as high as 26% in southern Sudan. Hepatitis D virus (HDV) relies on HBV for replication and can accelerate the progression of HBV-related liver diseases, leading to more severe outcomes. This study aims to determine the prevalence of HDV infection among Sudanese patients with HBV-related liver diseases and to investigate the clinical characteristics of patients with HDV co-infection.

Design/method: This descriptive cross-sectional hospital-based study was conducted in Sudan between June and September 2022. Ninety HBV patients aged 16 years and above were included. Patients were interviewed using a structured questionnaire, and medical histories and examinations were recorded. Investigations included liver function tests, abdominal ultrasounds, and ELISA for Anti-HDV IgG.

Results: In this study of 90 HBV patients, most were male (68.9%) and under 40 years old (58.9%). HDV-IgG antibodies were found in 8 patients (8.9%), all male. Among the HDV-positive patients, one (12.5%) had jaundice and one (12.5%) had ascites. Elevated ALT levels were seen in 50% of HDV-positive patients. One (12.5%) HDV-positive patient had low albumin. Cirrhosis was present in 25% of HDV-positive patients, and HCC was present in 12.5% of HDV-positive patient.

Conclusion: The prevalence of HDV infection among Sudanese patients with HBV-related liver diseases is 8.9%. This highlights the need for enhanced screening and diagnostic measures in Sudanese populations. Further research is needed to develop targeted interventions.

Keywords: hepatitis D virus, Sudan, super-infection, viral hepatitis

Introduction

Sudan is categorized as one of the nations where there is a high prevalence of hepatitis B surface antigen (HBsAg), exceeding 8%[1]. The prevalence of hepatitis B varies widely across different regions of Sudan, with rates ranging from 6.8% in central Sudan[2] to as high as 26% in southern Sudan[3]. HBV infection can lead to a variety of complications, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC).

The hepatitis D virus (HDV) relies on the presence of hepatitis B virus (HBV) for assistance in entering hepatocytes, facilitating intrahepatic spread, and transferring between hosts. Consequently, HDV acts as a satellite virus that necessitates HBV co-infection for replication. Additionally, HDV infection can hasten the advancement of HBV-related liver ailments, potentially accelerating more rapid development of cirrhosis and HCC, co-infection with HBV/HDV is correlated with a more severe disease progression and higher mortality rates when compared to having HBV monoinfection[4]. Certainly, ~50–70% of individuals with chronic HBV/HDV co-infection experience cirrhosis within 5–10 years following diagnosis, representing a threefold rise when contrasted with patients infected solely with HBV[5].

HDV, a single-stranded RNA virus, is classified as a defective virus that relies on the presence of HBV for complete expression and replication. Its discovery dates back to 1977 when Rizzetto *et al.*[6] in Italy first identified a new antigen-antibody system distinct from HBV, using direct immunofluorescence. The HDV genome is composed around 1700 nucleotides and is enveloped

HIGHLIGHTS

- Prevalence of hepatitis D virus (HDV) infection among Sudanese hepatitis B virus (HBV) patients: 8.9%.
- Predominance of HDV infection among young males.
- No significant differences in clinical characteristics between HDV-positive and negative patients.
- Importance of screening for HDV in Sudanese HBV patients.
- Need for targeted screening approaches and continued monitoring of at-risk populations.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:5091–5095

Received 19 April 2024; Accepted 23 June 2024

Published online 5 July 2024

http://dx.doi.org/10.1097/MS9.0000000000002337

by roughly 200 hepatitis D antigen molecules (HDAg). Furthermore, HDV strains are categorized into at least eight primary genotypes, each exhibiting distinct genome diversity and geographic distribution[7]. HDV-1 is the most commonly occurring genotype and is distributed across Europe, the Middle East, North America, and North Africa. HDV-2 to HDV-8 are region-specific. For example, HDV-2 is prevalent in countries such as Japan, Taiwan, and Russia. HDV-3, the most divergent genotype, is exclusively found in South America. HDV-4 has been reported in Japan and Taiwan, while HDV-5 to HDV-8 have been identified in Africa[8].

Infection with HDV and HBV can happen simultaneously (co-infection) or after initial HBV infection (super-infection)[9]. In co-infection, both HBV and HDV are present in the inoculum. The virulence of HDV relies on the virulence of HBV. Weak or slow HBV infection might result in an abortive HDV infection, while a strong and rapid HBV infection can facilitate HDV infection. Clinical acute hepatitis typically emerges 2–6 weeks after incubation. Co-infection leads to more frequent fulminant acute hepatitis (2–10%) than HBV alone (1%). Spontaneous death rates and HBV relapse after liver transplantation are lower in acute fulminant HBV/HDV hepatitis compared to HBV alone[10].

When a person with HBV is infected with HDV in a super-infection scenario, the HBV is already present in hepatocytes. The individual may be an inactive HBV carrier with minimal viral replication or liver damage, or they might have chronic hepatitis with HBV replication. Delta super-infection often results in a significant reduction or cessation of HBV replication, along with the appearance of anti-HBe antibodies, clearance of HBeAg, and undetectable HBV DNA, possibly leading to the disappearance of HBsAg. Conversely, markers of delta replication, such as anti-delta IgM and HDV RNA, become detectable[11].

The acute phase typically emerges 2–6 weeks after exposure, often causing extensive liver hepatocyte necrosis without a biphasic form. In individuals with an unknown chronic HBV carrier status, this episode might be misconstrued as acute hepatitis B or B/delta co-infection. When chronic HBsAg carriage is known, it could indicate HBV reactivation or HBeAg seroconversion. Therefore, testing for delta serology in all HBV carriers is crucial. In cases of delta super-infection, fulminant presentations are more prevalent, with an estimated 15% risk and a high proportion of chronic delta hepatitis, ~80%. Chronic delta hepatitis is believed to induce more severe histopathological liver damage than HBV, leading to rapid progression to cirrhosis and hepatocellular carcinoma[12].

Similar to HBV, HDV is transmitted through the parenteral route by exposure to infected blood or body fluids. Only an extremely small inoculum is required to transmit the infection[13].

The clinical scope of HDV infection varies, spanning from an inactive asymptomatic carrier state to acute liver failure. Co-infection of HBV and HDV commonly results in a mild self-limited illness, though severe acute hepatitis with spontaneous resolution of both infections is less likely. Conversely, HDV super-infection in chronic HBV carriers often entails a prolonged clinical trajectory. However, patients demonstrate diverse clinical manifestations, with more severe disease observed in genotypes 1 and 3, intravenous drug users, and older patients in European cohorts[14].

Screening for HDV should be contemplated in all patients positive for HBsAg, particularly those exhibiting deteriorating liver function. Initially, it is advisable to test for total anti-HDV antibodies (IgM and IgG) using EIAs or radioimmunoassays[14].

The rate of HDV seroprevalence varies across different parts of the world. Out of the 350 million people with chronic HBV infection, ~15 million individuals show serological evidence of exposure to HDV[15]. HDV seroprevalence does not consistently align with HBV seroprevalence. For instance, while 90% of HBV carriers in the Pacific Islands are infected with both viruses, the rates drop to 8% in Italy and 5% in Japan[16]. HDV infection is endemic in various regions, including the Middle East, Central Africa, the Horn of Africa, the Mediterranean, Eastern Europe, the Amazon Basin, and parts of Asia[17]

Recent estimations indicate HDV prevalence in sub-Saharan Africa ranging from 1.3 to 50%[18]. Despite the endemic nature of HBV in Nigeria, there is limited data on HDV seroprevalence. A previous study revealed detectable HDV antigen in 6.5% of patients with chronic hepatitis B in Southwest Nigeria[19].

This study aims to determine the prevalence of HDV infection among Sudanese patients with HBV-related liver diseases and to investigate the clinical characteristics of patients with HDV co-infection.

Patient and methods

A descriptive cross-sectional hospital-based study was conducted at a tertiary facility specializing in gastrointestinal and liver diseases, with a liver clinic established in 2000. The clinic offers medical care, follow-up services, and patient education. The study, conducted between June and September 2022, enrolled all adult patients (aged 16 years and above) with hepatitis B virus infection who met the inclusion criteria and presented at the liver clinic or were admitted to the hospital during the study period. Patients with co-infection of HIV and HCV were excluded. The work has been reported in line with the STROCSS criteria[20].

Patients were personally interviewed using a structured questionnaire. Detailed medical histories were recorded, and thorough examinations were performed for each patient. Investigations included liver function tests, abdominal ultrasounds to identify features of chronic liver disease, and evidence of decompensation. ELISA for Ant-HDV-IgG was conducted.

Blood samples from each patient were analyzed for the presence of HDV-IgG using a commercially available enzyme-linked immunosorbent assay kit ("HDV-IgG ELISA" kit) for qualitative determination of IgG antibodies to the hepatitis D virus in human serum or plasma. The assays were performed according to the manufacturer's instructions, with two positive and three negative controls included in each assay. As per the information in the kit's insert, the immunoassay used has been determined to have 100% sensitivity and specificity.

Statistical analysis

Results are expressed as frequencies and percentages. Descriptive statistics were employed to determine the incidence of hepatitis D infection in Sudanese's patients with hepatitis B infection among the Sudanese patient. Univariate analysis was conducted. Categorical variables such as patient demographics and medical history were assessed using χ^2 Test. Continuous variables were analyzed using *t*-tests depending on the distribution of the data. All statistical analyses were conducted using statistical package

for social sciences (SPSS), version 26.0. A two-sided p value of less than 0.05 was considered statistically significant for all analyses.

Ethics

All patients were provided with informed consent to participate in the study, and only those who agreed were included. Permission was obtained from the Gastroenterology Council Research Committee and the hospital authority.

Results

Ninety HBV patients were included in this study, with 62 patients being male (68.9%) and 28 (31.1%) being female. Most of the patients (58.9%) were under 40 years old, 17.8% were between 40 and 50 years, and 23.3% were over 50 years old (Fig. 1). HDV-IgG antibody was positive in 8 patients (8.9%) (Table 1), all of whom were male, with a p value of 0.046 (Table 2).

Among the HDV-negative patients, 16 (19.5%) had jaundice, while one (12.5%) of the HDV-IgG-positive patients had jaundice, with a p value of 0.63 (Table 2). Furthermore, 9 (11%) of the HDV-negative patients had ascites, while one (12.5%) of the HDV-IgG-positive patients had ascites, with a p value of 0.90 (Table 2). Alanine transaminase (ALT) was elevated in 18 patients of the HDV-negative group (21.9%) and in 4 of the HDV-IgG-positive patients (50%), with a p value of 0.78 (Table 2). Among the HDV-negative patients, 16 (19.5%) had low albumin, whereas one (12.5%) of the HDV-IgG-positive patients had low albumin, with a p value of 0.63 (Table 3). On liver ultrasound, 19 (23.2%) of the HDV-negative patients had cirrhosis and 2 (2.4%) had HCC, while 2 (25%) of the HDV-IgG-positive patients had cirrhosis and one (12.5%) had HCC, with a p value of 0.31 (Table 3).

Discussion

The study population consists mostly of males (68.9%) and is relatively young, with 58.9% being under 40 years old. This trend aligns with findings from a study conducted in Libya by Elzouki *et al.*[21], where the mean age of patients was 36.92 ± 15.35, with 63.6% of them being male. A similar pattern was observed in a study conducted in Accra, Ghana, by Asmah *et al.*[22], where males constituted 73.6% of the population, and the mean age of patients was 38.6 years.

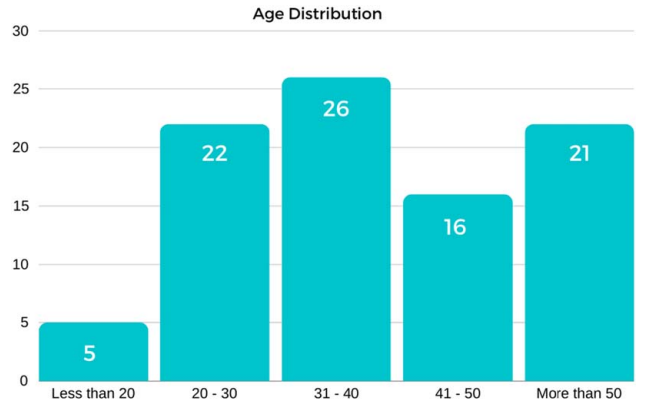

Figure 1. Bar chart illustrating the distribution of patients by age groups.

Table 1

Prevalence of Anti-HDV IgG Antibodies.

Anti-HDV IgG	Frequency	Percent (%)
Positive	8	8.9
Negative	82	91.1
Total	90	100.0

HDV,hepatitis D virus; IgG, immunoglobulin G.

The prevalence of anti-HDV in our study (8.9%) falls within the range reported in previous studies from the region and beyond. Similar findings were observed in Eastern Sudan (9%)[23], Nigeria (6.5% HDV antigen)[24], Saudi Arabia (8%)[25], and Tehran, Iran (7.7%)[26]. However, our results are lower than those reported in central Sudan (27.8%)[27] and higher than those from Egypt (4.7%)[28] and Libya (2.5%)[21].

In this study, all the patients with a positive HDV-IgG antibody were male (p value 0.046). This finding is consistent with a study conducted in Accra, Ghana, by Asmah *et al.*[22], where the proportion of males with anti-HDV positivity was 9.4% compared to 1.9% in females, although the difference was not statistically significant ($P = 0.350$). It is also similar to the results of a study conducted in Turkey by Kose *et al.*[29], which indicated that 43% of the subjects were female and 57% were male.

There was no statistically significant difference in the clinical, biochemical, and radiological characteristics between HDV-IgG antibody positive and negative patients (jaundice p value 0.63, ascites p value 0.90, ALT p value 0.78, albumin p value 0.63, cirrhosis, and HCC p value 0.31). This contradicts the findings of a study conducted in Egypt by Gomma *et al.*[28], where serum ALT levels in HBsAg/anti-HDV-positive cases were elevated in comparison to anti-HDV-negative cases (55.6 ± 38.0 IU/l in dual infection versus 40.1 ± 26.0 in anti-HDV-negative cases). Similarly, the study conducted in Libya[21] demonstrated a significant association between HDV seropositivity and elevated serum ALT ($P = 0.03$), elevated serum AST ($P = 0.04$), and the

Table 2

Correlation between Anti-HDV IgG and gender, jaundice development, ascites, and elevated alanine transaminase (ALT) levels.

	Anti-HDV IgG				
Variable	**Positive**		**Negative**		***P***
Sex					
Male	8	8.9%	54	60%	0.046
Female	0	0.0%	28	31.1%	
Jaundice					
Developed	1	1.1%	16	17.8%	0.63
Not developed	7	7.8%	66	73.3%	
Ascites					
Developed	1	1.1%	9	10%	0.90
Not developed	7	7.8%	73	81.1%	
Alanine transaminase (ALT)					
Normal	4	4.4%	64	71.1%	0.78
High	4	4.4%	18	20%	

HDV, hepatitis D virus; IgG, immunoglobulin G.

Table 3

Comparison between HDV-negative and HDV-positive patients.

	Low albumin (%)	Cirrhosis (%)	HCC (%)
HDV-negative	19.5	23.2	2.4
HDV-positive	12.5	25.0	12.5

HCC, hepatocellular carcinoma; HDV, hepatitis D virus.

presence of cirrhosis ($P = 0.003$). This discrepancy might be due to the larger sample sizes in these studies, as well as the fact that most of our patients were asymptomatic and referred to our clinic after testing positive for HBsAg during blood tests for employment or travel. Our results are comparable to those of a study conducted in Vietnam by Hung Minh Nguyen *et al*., which showed that aminotransferase enzymes (ALT and AST: 43.6 IU/l and 35.0 IU/L vs. 43.5 IU/l and 36.3 IU/l, respectively; $P > 0.05$), as well as total bilirubin (8.5 vs. 8.7 μmoL/l) and direct bilirubin (3.5 vs. 3.4 μmoL/l), were not significantly higher in HDV-positive compared to HDV-negative HBV-infected patients ($P > 0.05$)[30].

This study is limited by its relatively small sample size of 90 participants. Recruitment efforts were hampered by the ongoing conflict within Sudan, which restricted access to potential study participants. Additionally, the cost of the specialized HDV-IgG ELISA kits presented a financial constraint.

Despite these limitations, this study represents the first investigation into the prevalence of HDV co-infection among Sudanese patients diagnosed with HBV-related liver diseases. These findings provide valuable preliminary data on the potential burden of HDV in this population. Future research efforts are warranted to confirm these results with larger, more geographically diverse cohorts. Such studies would benefit from the inclusion of additional data points, such as HDV genotype and potential risk factors for HDV infection.

Conclusion

This study in Sudan examined how often HDV co-infects people with HBV. Among 90 HBV patients, 8.9% also had HDV, similar to rates reported elsewhere in the region. The study group was mostly male and young, which is typical for HBV. Surprisingly, there were no significant differences in symptoms, lab tests, or scans between those with and without HDV. This could be due to the small number of participants or because many were asymptomatic. Limitations include the sample size being limited by conflict and cost. Future research with more people from different areas of Sudan is needed to confirm these findings and understand HDV risk factors in this population.

Ethical approval

Ethical approval was obtained from the Gastroenterology Council Research Committee and the hospital authority.

Patient consent

Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

M.A.: study concept, data collection, writing the paper. B.A.: study concept, data collection, writing the paper. A.R.: study concept, writing the paper. A.A.: supervision, critical revision.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

Clinicaltrials.gov Identifier: NCT06360484.

Guarantor

Ahmed Rafei.

Data availability

Not available.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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