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Clinical Presentation of Chronic HBV Infection Among Sudanese Patients at A Tertiary Hospital: A Cross-sectional Study

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Keywords
Clinical Presentation, Hepatitis B, Sudan, Tertiary hospital.

Abstract
Background:HBV (HBV) infection is one of the major health problems in Sudan and throughout the world.
Aims: We aimed to identify the characteristics of patients having a chronic hepatitis B based on the initial and follow-up clinical evaluations.
Setting and design: Methods and Material: This is a cross-sectional descriptive analysis of clinical and laboratory data of adults' chronic carriers of HBsAg, not exposed to treatment, with at least two outpatient consultations, between April 2020 and August 2020 in the hepatology outpatient clinic of the Ibn SinaSpecialised Hospital, Sudan.
Statistical analysis:We conducted data analysis by using the computer program Statistical Package for Social Sciences (SPSS) version 23(IBM Corp., Armonk, NY, USA). Results obtained were presented in tables and figures. Frequencies and percentages were used in the tables.
Results: A total of 98 consecutive patients were included in the study, we find that (84.7%) of patientshadnegative(HBeAg), (1%) had hepatitis C coinfection, (4.1%) had cirrhosis, and (1%) had

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hepatocellular carcinoma, while (77.6%) of them had a viral load of ≥ 2000 IU/ml.Conclusion: Chronic hepatitis B infection in Sudan is one of the health problems that occurred in middle and low socioeconomic status.

1. Introduction

HepatitisB virus (HBV)infection is a global health problem with over 350-400 million people being chronic carriers of HBV surface antigen. Out of these numbers, 65 million reside in Africa which represents 18% of the global burden of HBV infection. In addition to the difficulties encountered in controlling the spread of the disease, HBV remains a health hazard partly because the viral exhibits different genotypes and sub-genotypes in different geographic regions of the world.[1]Sudan is classified among the countries with high HBV seroprevalence ranging from 8% in central Sudan to 26% in previous Southern Sudan, with the virus being the commonest cause of chronic liver disease and hepatocellular carcinoma and the second commonest cause of acute liver failure.[2]The natural prognosis of the infection depends on several aspects, such as geographical location, age at initial infection, viral genotype, host immune system, association with alcoholism, steatosis, and coinfections such as hepatitis C and D.[3] HBV is a small, enveloped virus containing partially double-stranded DNA. The DNA and HBV-specific DNA polymerase are surrounded by the HBV core antigen (HBcAg), which in turn is surrounded by a lipoprotein envelope containing the HBV surface antigen (HBsAg). The serum of patient infected with HBVcontains complete virus particles, as well as non-infectious spherical or filamentous HBsAg particles. Acute form of hepatitis B is characterised by the appearance of serum HBV markers, including HBsAg and Immunoglobulin M (IgM) anti-HBc, which then disappear during convalescence. The persistence of HBsAg for more than 6 months indicates a chronic infection. Chronic hepatitis B develops in 90% of new-borns who become infected, compared with 29–40% of children and 5–10% of adults infected. The immune status of the infected person also influences the development of chronic hepatitis. Chronic HBV infection can be diagnosed by serology (identification of HBsAg and HBV DNA), biochemistry (elevated aminotransferase levels), and liver biopsy. Liverbiopsy is an important indicator to assess the severity of the disease, its stage, prognosis, and to exclude other forms of hepatic diseases. The outcome of chronic HBV infection varies between individuals, with estimated 5-year survivals of 97% for chronic persistent hepatitis, 86% for chronic active hepatitis, 55% for chronic active hepatitis with cirrhosis and 25-60% for hepatocellular carcinoma.[4] The accurate evaluation of these markers in combination with clinical assessment and liver enzyme estimation enables the evaluation of natural history and individual risk of progressive liver disease and forms the basis of national and international management guidelines.[5]

We aimed in this study to determine and characterised the forms of clinical presentation of an outpatient cohort of chronic hepatitis B as per initial and follow-up parameters.

2. Materials and Methods

This is a cross-sectional prospective hospital-based study. The study was conducted at the hepatology outpatient clinic in Ibn Sina specialised hospital, Sudan during the period from April 2020 to August 2020 with the duration of 4 months.We included all patients with chronic HBV infection who presented to the outpatient clinic during the study period. We included patients with chronic HBV infection (HBsAg positive for > 6 months) and all patients who accepted to contribute in the study. We excluded patients who did not had a chronic hepatitis B, patients had other forms of hepatitis, and patients refused to join the study.The sample size of this study was 98 patients. We used a total coverage sampling technique to select patients who meet the inclusion and exclusion criteria and presented to the study area during the study period.Data was collected using a constructed questionnaire to analyse the clinical, radiological, and laboratory data from chronic HBsAg positive adults in the hospital and during the study period.

Statistical analysis:

We conducted data analysis by using the computer program Statistical Package for Social Sciences (SPSS) version 23(IBM Corp., Armonk,

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NY, USA). Results obtained were presented in tables and figures.Frequencies and percentages were used in the tables.

Ethical considerations:

Before the commencement of taking information from each patient, we explained to them the direct benefit for the participants along with the risk factors of HBV infection transmission and the possible complications of the disease. We rigorously observed the privacy of the patients with total confidentiality for their information. Then voluntary informed written consent was obtained from the participants. Ethical clearance was obtained from the ethical committee at the research unit EDC and hepatology department at Ibn Sina specialised hospital, Sudan.

3. Results

A total of 98 Sudanese patients with chronic HBV infection who satisfy the inclusion and exclusion criteria were included in this study. The study found that more than three-quarters of the patients were married, while (20.4%) of them were single, (2%) were divorced and (2%) were widows. The socioeconomic status of the participants ranged between low (56.1%) and medium (43.9%) based on their jobs and their ability to afford medications, however, nearly three-quarters of them had a medical insurance. We found that three quarters of the patients had no social habits, whereas 15.3% of the patients were smokers and 5% of them were alcoholic and smokers(Table 1).

Table 1: Frequency distribution of patients according to their marital, socioeconomic, medical insurance status, and social habit (N=98).

Character		Frequency (%)
Marital Status	Single	20 (20.4%)
	Married	74 (75.5%)
	Divorced	2 (2%)
	Widowed	2 (2%)
Socioeconomic status	Low	55 (56.1%)
	Medium	43 (43.9%)
Medical insurance	Yes	73 (74.5%)
	No	25 (25.5%)
Social habit	Cigarette smoking	15 (15.3%)
	Alcohol+ Cigarette smoking	5 (5.1%)
	Alcohol	4 (4.1%)
	No	74 (75.5%)

The risk factors assessment of the patientsrevealed that more than two thirds of patients did not recall a specific risk factor, nearly one fifth of them had a history of contact with an infected patient, while the rest were exposed to other risk factors such as the history of surgical operations, blood transfusion (9.18%), health workers (1%), sharing sharp objects and haemodialysis(2%) (Table 2).

Table 2: Frequency distribution of patients according to their past medical history of significant risk factors (N=98).

Risk factor	Frequency (%)
History of contact with infected patient	19 (19.3%)
History of surgical operations or blood transfusion	9 (9.18%)
Others (hemodialysis, sharp objects ... etc.)	2 (2.04%)
Health care workers	1 (1.02%)
Did not recall a specific risk factor	67 (68.4%)
Total	100 (100%)

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The initial clinical presentation of the participants showed that (71.4%) of them were asymptomatic and accidentally discovered, (9.2%) presented with variceal bleeding, (6.1%) with jaundice, (2%) with ascites, (2%) with hepatocellular carcinoma and (1%) with hepatic encephalopathy. Several patients had a more complicated presentation in a form of variceal bleeding and ascites in (3.1%) and (2%) presented with ascites and spontaneous bacterial peritonitis (Table 3).

Table 3: Frequency distribution of patients according to their initial clinical presentation (N=98).

Patient presentations	Frequency (%)
Asymptomatic	70 (71.4%)
Variceal Bleeding	9 (9.2%)
Jaundice	6 (6.1%)
Variceal Bleeding plus Ascites	3 (3.1%)
Ascites	2 (2%)
Hepatocellular Carcinoma	2 (2%)
Jaundice plus Ascites	2 (2%)
Ascites plus SBP	2 (2%)
Hepatic Encephalopathy	1 (1%)
Variceal Bleeding plus Jaundice plus Ascites	1 (1%)
Total	100 (100%)

Regarding participant's co-morbidities, we found that (11.2%) of them had diabetes, (10.2%) had hypertension, (1%) have a combination of diabetes and hypertension, Parkinson's disease (2%), rheumatic heart disease (1%), schistosomiasis (1%), chronic kidney disease (1%), and pulmonary tuberculosis (1%) (Table 4).

Table 4: Frequency distribution of patients according to their other comorbidities (N=28).

Disease	Frequency (%)
Diabetes Mellitus	11 (11.2%)
Hypertension	10 (10.2%)
Parkinson	2 (2%)
Rheumatic heart disease	1 (1%)
Bilharziasis	1 (1%)
Chronic kidney disease	1 (1%)
Pulmonary tuberculosis	1 (1%)
Diabetes + Hypertension	1 (1%)
Total	28 (28.6%)

The initial serological workup of the participants indicates that most of patients (86.7%)had a normal Alanine transaminase (ALT). Nearly three-quarters of the patients had normal serum bilirubin, while one-quarter of them had high serum bilirubin. The abnormal serum bilirubin further divided into (28%) mainly direct bilirubin and (72%) mainly indirect bilirubin. We identified (15.3%) of patients had low serum albumin indicating chronic liver disease(Table 5).

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Table 5: Frequency distribution of patients according to their biochemical parameters (N=98).

Biochemicalparameters		**Frequency (%)**
Serum ALT	Normal*	85 (86.7%)
	Abnormal	13 (13.3%)
Serum bilirubin	Normal**	74 (74.5%)
	Abnormal	25 (25.7%)
	Abnormal indirect bilirubin	18 (72%) †
	Abnormal direct bilirubin	7 (28%) †
Serum albumin	Normal**	83 (84.7%)
	Abnormal	15 (15.3%)

*Normal serum ALT level is up to 56 U/L.
**Normal serum bilirubin level is up to 1.2 mg/dl.
***Normal serum albumin level range between 3.4-5.4 gm/dl.
† Out of 25 patients.

(15.3%) had positive HBeAgserostatus and (84.7%) had negative HBeAgserostatus at presentation. (19.4%) had an undetectable viral load (HBV DNA) at presentation, while (77.6%) had a viral load of ≥ 2000 IU/ml (Table 6).

Table 6: Frequency distribution of patients according to HBeAg andHBV DNA levels (N=98).

Serostatus	**Frequency (%)**
HBeAgPositive	83 (84.7%)
HBeAgNegative	15 (15.3%)
HBV DNA levelUndetectable	19 (19.4%)
HBV DNA level<2000 IU/ml	3 (3.1%)
HBV DNA level>2000 IU/ml	76 (77.5%)

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Regarding the ultrasound scans of the participants, (62.2%) had normal scans, while (37.8%) had abnormal scans. Out of the abnormal scans, (4.1%) had liver cirrhosis, (4.1%) had periportal fibrosis, (3.1%) had fatty livers, (1%) had focal lesions (hepatocellular carcinoma), (2%) had portal hypertension, (32.7%) had splenomegaly and others had different combinations of those findings (Table 7).

Table 7: Frequency distribution of patients according to U/S findings (N=98).

Findings	Frequency (%)
Normal Ultra Sound scan	61 (62.2%)
Abnormal Ultra Sound scan	37 (37.8%)
Liver cirrhosis	4 (4.1%)
Periportalfibrosis	4 (4.1%)
Fatty liver	3 (3.1%)
Portal hypertension	2 (%)
Gallstones	1 (1%)
Focal lesions	1 (1%)
Para-aortic Lymph Nodes	1 (1%)
Portal vein thrombosis	1 (1%)

Fibro scan was done in only one patient and upper GIT endoscopy was done for 22 patients with different findings including grade 1-3 oesophageal varices with or without portal hypertension gastropathy and fundal varices (Table 8).

Table 8: Frequency distribution of patients according to endoscopy findings (N=98).

Findings	Frequency (%)
G III oesophageal varices	11 (11.2%)
G II oesophageal varices	8 (8.1%)
G I oesophageal varices	2 (2%)
No varices in the oesophagus	1 (1%)
No endoscopy scan	76 (77.6%)
Total	98 (100%)

4. Discussion

Chronic infection with HBV is a dynamic and complex process of interaction between the virus, the hepatocytes, and the host immune system. The variability in the forms of presentation of the disease, both individually and collectively, represents a great challenge in patient management and in public health.

In this study, we included 98 subjects and attempted to shed light on the clinical and biochemical characteristics in a Sudanese cohort of hepatitis B patients.In many parts of sub-Saharan Africa, the serological characteristics of hepatitis B infection have not been firmly established. There are even fewer studies on the quantification of HBV viral load in infected populations, due to the limited availability of molecular technology and the cost of molecular testing.[6]

The increase in the prevalence of seronegative HBeAg is a worldwide tendency. A review study conducted in the Middle East described a 53-90% prevalence of this profile. A Spanish study revealed that 87.8% of 474 patients were HBeAg non-reactive, a proportion described as like that of other Mediterranean countries. A serologic inquiry with Americans of Asian origin showed a 90% prevalence of the profile. Two Brazilian studies also demonstrated a higher frequency of HBeAg negative: 84.4% of 521 patients in the Southeast region and 53.4% of 1,448 patients in regional reference centres

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of liver diseases. Similarly, there was a predominance of this profile (84.7%) of the patients in our study. In conformity with the literature, the results of our study suggest greater unpredictability of the evolution of HBeAg non-reagent patients. Determination of the presentation forms of the disease was more complex in the presence of this serological profile, and all the divergences found by analysis of the admission parameters occurred in this group.[7]

It is notable that more than half of the subjects who were HBeAg-negative had a high-level HBV replication. This finding has been termed HBeAg-negative hepatitis and is the predominant form of chronic hepatitis B–and associated liver disease in Asia and sub-Saharan Africa. The distinction between chronic inactive carriers and patients with HBeAg-negative disease has a decisive impact on patient care decisions. The active viral replication in the latter represents the strongest single predictive biomarker associated with disease progression and is attributed to the activity of HBV viral mutations that replicate aggressively without generating the HBeantigen with HBeAg-negative disease that requires treatment evaluation and may require antiviral therapy for disease control.[6]Another challenge in resource-limited countries like Sudan is the affordability of antiviral treatment. This becomes important in the treatment of HBeAg-negative patients; as the treatment end-point is not clear.

Research in endemic areas has already demonstrated a weak correlation between viral load and transaminases, in our study, there is no significant correlation between them (P = 0.35). From another perspective, almost all asymptomatic patients had normal ALT level (87.7%) which emphasise the importance of checking the viral load as we couldn't depend on the ALT alone in the treatment process. In the currently available guidelines, the recommendation is that HBV DNA, ALT, and HBeAg should be analysed together and with great care for the indication of the biopsy and therapy decision-making. The most recent international guidelines also point out the need for multiple clinical applications with repeated measurements of transaminases and HBV DNA for the determination of the phases of the disease and better management of the infected patients.[7]

Upper GIT endoscopy was done in about one-quarter of our study population (22.4%). oesophageal varices were found in all these patients, except one. Only 9 of those were presented with upper GI bleeding, the rest had decompensated liver disease without bleeding, which emphasises that the Ibn Sina hepatology department is following proper policies and guidelines.

The primary limitations of this study were its retrospective character which results in deficiencies in the process of data collection, the lack of performance regarding fibro scan and liver biopsy to determine the degrees of fibrosis, the absence of molecular studies to assess the commonest genotype and the correlation with liver cirrhosis and HCC. Within this context, our results, corroborated by literature, suggest that due to the dynamism of the chronic infection by HBV, the infected patients should be continuously and carefully evaluated, as per the joint analysis of the clinical, biochemical, molecular biology, and sometimes histologic parameters.

This study suggests future research be conducted in the area of hepatitis B and C viral infections with the regard to the seronegative and accessibility to health services in order to prevent these serious infections.

5. Conclusion

Chronic hepatitis B infection in Sudan is usually found in the middle age group in contrast to the literature, most likely due to their higher exposure to medical care. There is also male predominance, mostly uneducated with low socio-economic status. The majority are HBeAg non-reactive with a significant association between age and decompensated liver cirrhosis. There was a weak correlation between viral load and trans-aminases with normal ALT levels in most of the study population. Almost all patients with decompensated liver disease whether presented with upper GI bleeding or not underwent upper GI endoscopy and were found to have oesophageal varices.

We recommend an increase in public awareness to educate people about different modes of transmission and risky behaviours. Moreover, tight infection control measures should be applied in different health providing sectors as well as vaccine. Funds and support should be directed towards

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different facilities like molecular studies and fibro scans to increase the accuracy of the management process.

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Conflicts of Interest
The authors declare no conflict of interest.

Institutional Review Board Statement
Ethical clearance was obtained from the ethical committee at the research unit EDC and hepatology department at (Ibn Sina) specialised hospital, Sudan, Number (112.19.02)

Informed Consent Statement
Before the commencement of taking information from each patient, we explained to them the direct benefit for the participants along with the risk factors of hepatitis B infection transmission and the possible complications of the disease.
We rigorously observed the privacy of the patients with total confidentiality for their information. Then voluntary informed written consent was obtained from the participants.

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