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HBV HCV Co-Infection: A Dual Threat

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ABSTRACT

Background: The global HBV-HCV co-infection prevalence is estimated between 3%-30%. Such co-infected patients have a severe liver disease & and higher chances of hepatocellular carcinoma compared to mono infections. Moreover, many patients with Hepatitis B or Hepatitis C are incidentally diagnosed thus making it difficult to gauge the actual prevalence of the infection. Adding to the woes is the fact that screening hepatitis B only with Hbs Ag will underdiagnose many HBV-HCV co infected patients. It is widely believed that HCV is dominant over HBV. However, HBV can be the dominating virus in co-infections as observed in our case report.

Case Presentation: Two middle-aged patients having chronic kidney disease and on dialysis with a past history of surgery and blood transfusion were diagnosed incidentally with HBV HCV co-infection. None of them had taken any treatment for either viruses prior to this. One case showed a dominance of HBV while other showed the dominance of HCV. Both patients had HCV Genotype 1a while HBV genotyping could not be done. Both patients died within 6 months of diagnosis.

Conclusion: Screening must be ensured for both HBV & HCV in patients with common risk factors. Either HCV or HBV can be the dominant virus in case of a co-infection. Patients with HCV as the dominant virus may have a higher APRI and FIB-4 score.

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Introduction

The World Health Organisation (WHO) estimates that 350 million people are affected with Hepatitis B Virus (HBV) and 170 million are affected with Hepatitis C Virus (HCV) all over the world.Since both HBV and HCV have common modes of transmission,co-infections are not rare. HBV & HCV can be transmitted simultaneously or can occur as a superinfection (HCV superinfection being more common than HBV superinfection) [1,2]. The prevalence rate of HBV-HCV co-infection is estimated to have a wide range of 3% to 30% [1-5]. The prevalence of occult HBV infection in HCV infected patients ranges from 11.9% to 44.4% [2].

As compared to mono-infected patients, co-infections tend to have a more severe liver disease & a higher incidence of hepatocellular carcinoma [2-4]. Testing for Hbs Ag alone in HCV infected patients may underestimate the prevalence of HBV HCV co-infection since occult HBV infections are known to occur, the frequency being higher in HCV co-infected patients [4-6]. All patients diagnosed with HCV should be tested for HBV using HbsAg, Anti HBs and Anti HBc [7]. Either virus can play a dominant role, thereby making it essential for screening for both viruses in people having common risk factors [3].

APRI is a non-invasive tool for the assessment of liver fibrosis in Chronic hepatitis [8]. Though liver biopsy is the gold standard for assessment of liver fibrosis FIB-4 serves as a non-invasive tool for the same [9].

Materials & Methods

For Diagnosis of HCV

Patients visiting AIIMS Jodhpur were enrolled in the study. Three millilitres of blood sample was collected in serum separator gel tube and the serum was tested for Anti-HCV antibodies by rapid immunochromatography (SD Biosensor). The samples which tested Reactive for Anti-HCV antibodies were confirmed by ELISA (Trustwell) which detects total Anti-HCV antibodies by using recombinant HCV antigens (Core , NS3,NS4,NS5) using the principle of sandwich Enzyme immunoassay [10].

If the samples tested reactive by ELISA also, an extra blood sample in EDTA vial was collected for the quantitative estimation of HCV RNA after taking written and informed consent. Two EDTA vials were collected with 4 ml blood each and centrifuged at 3000 rpm for 5 minutes. The plasma was separated and stored at minus 80 degrees Celsius till further testing. Extraction of HCV RNA was done using the Abbott m2000 sp system using the 0.2 ml protocol and PCR was done using Abbott m2000 rt,the Lower limit of detection (LLOD) of which is 30 IU/ml.

HCV Genotyping
HCV Genotyping was done using TRUPCR HCV Genotyping kit (Real time based detection of HCV genotypes 1, 1a, 2(2a/2b),3,4,5a &6.

Genotyping was done at a later date than HCV viral load. Extraction for which was was done using TRUPCR total viral nucleic acid extraction kit.

For Diagnosis of HBV
The same serum sample which was used for detection of Anti-HCV antibody was used for detection of HbsAg by rapid immunochromatography (Fastvue). If the sample tested positive, it was further subjected to HbsAg ELISA (BIORAD) to rule out false positive cases.Those patients who tested positive by ELISA for HbsAg were included in the study.

Viral load for HBV was determined using Diagsure HBV viral load kits (Limit of detection: 10 IU/ml) using the same EDTA sample as for HCV. Extraction was done using TRUPCR total nucleic acid extraction kit.

APRI Score
For calculation of AST to platelet ratio index (APRI) score, the following formula was used [11]:

{[AST(IU/L)/AST (Upper Limit of Normal) (IU/L)] / Platelet count (109/L)} X 100

FIB-4 Score
For calculation of Fibrosis-4 score (FIB-4), the following formula was used:

{[Age(years) X AST Level (IU/L)] / [Platelet count (109/L) X √ALT(IU/L)]} X 100 [12].

Case Histories
Case 1
A 56-year-old non diabetic male, farmer by occupation, case of chronic kidney disease (CKD) stage 5 on maintenance hemodialysis twice per week for 10 months presented to Adult Intensive Care Unit with mild ascites & altered sensorium. He had a history of 10 units of blood transfusion. History of kidney calculus and underwent surgery for the same twice over a period of 2 years. He did not give any history of jaundice or fever. He had no other risk factors such as tattoo or intravenous drug abuse. It was an incidental diagnosis of HBV HCV co-infection. He had never taken any HBV or HCV treatment prior to this.

Case 2
A 48-year-old non diabetic female, presented to AIIMS jodhpur, who was a known case of chronic kidney disease stage 5, was on hemodialysis for two years, twice per week. She had Right brachiocephalic arteriovenous fistula with pseudoaneyrysm in draining cephalic Vein. History of AV fistula (AVF) 2 months ago, after 6 cycles of Hemodialysis via fistula complain of swelling due to immature intitiation of AVF. She was advised ligation of Right Brachiocephalic AVF and draining cephalic Vein.

Thus, both patients were incidentally diagnosed with HBV HCV co-infection and both had a high viral load of Hepatitis C genotype 1a.

Table 1: Table Showing the Viral Load and Risk Factors of the Patients

Sr No.	Age/Sex	HCV Viral load (Abbott) IU/ml	HCV GT (TRUPCR)	HCV treatment	HBV Viral load (Diagsure) IU/ml	HBV treatment	Risk factors
1	56/Male	7.2 $X10^6$	1a	Nil	3.9x 10^8	Nil	CKD# 5, Dialysis for 10 months, twice per week, Blood transfusion, Renal stone surgery
2	48/Female	1.5$X10^6$	1a	Nil	510	Nil	CKD# 5, On dialysis for 2 years, twice per week Blood transfusion, History of cataract surgery

Chronic Kidney Disease

Table 2: Lab Parameters of the Patients

Sr No	Total Bilirubina mg/dl	AST[b] IU/ml	ALT[c] IU/ml	ALP[d] IU/ml	APRI[e]	FIB4[f]
1	0.73	39	19.4	317	0.79	3.99
2	0.39	18	13.6	327	0.19	1.03

[a]Normal Total Bilirubin range(milligrams/decilitre): 0.3-1-2
[b]Normal Aspartate Aminotransferase (AST) range (International Units/millilitre): 0-50
[c]Normal Alanine Aminotransferase (ALT) range (International Units/millilitre): 0-50
[d]Normal Alkaline Phosphatase (ALP) range: 30-120
[e]AST to Platelet Ratio Index
[f]FIB4: Fibrosis-4 score

Discussion

Patient 1, who was a 56-year-old male, had multiple risk factors like dialysis, blood transfusion & a history of previous surgery. He tested non-reactive for HIV antibodies by rapid immunochromatography. HBV viral load in this patient was higher compared to HCV viral load. Thus, HBV was dominant in this patient. Also,the APRI and FIB-4 score was higher compared to the second patient.

Patient 2, was a 48-year-old female, had chronic kidney disease stage 5, was on dialysis & had a history of fistula surgery. Her duration of dialysis was longer compared to the first patient. She tested non-reactive for HIV antibodies by rapid immunochromatography. She had a higher viral load of HCV compared to HBV. Thus HCV was dominant over HBV. Moreover, her FIB-4 and APRI score was lower compared to the first patient.

Both cases were incidental diagnosis of HBV HCV co-infection. Both patients expired after 6 months of diagnosis. Medical records for treatment were not available.

Most authors report HCV dominance over HBV but our case reports have shown HBV dominance over HCV. Since this is a cross-sectional observation, it is possible that dominance of the two viruses may change over the course of the disease.

Moreover, the Genotypes of both HCV in our case reports was 1a. The genotype of HBV could not be determined. It would be interesting to see if the genotypes of the two viruses have anything to do with viral dominance given that India is endemic for both viurses. Such patients need to be followed up to see if the dominance changes over the life cycle of the two viruses.

The anti-viral efficacy remains unaffected in HBV HCV co-infection [13].

Limitations

Based on a case series of two patients it is not possible to draw a conclusion for the general population. Moreover, such patients need a follow up till the end of treatment & beyond to understand the dynamics of co-infection. HBV is known to get reactivated after successful treatment for HCV.

HBV infected patients should have been screened for Hepatitis D also. Moreover, the genotype of HBV would have given a better picture regarding viral interactions. The gold standard for determining HCV genotype remains Next Generation Sequencing.

Conclusion

Since both HBV and HCV have the same mode of transmission, it is crucial that screening is done for both hepatotropic viruses for patients with risk factors, even if the patient is asymptomatic clinically and the lab parameters like Liver function tests are within the normal range. Screening for HbsAg alone may not be sufficient hence other HBV viral markers should also be tested for. Also, on comparing the two patients, it appears that HCV dominance over HBV can lead to a higher AST, ALT levels. Also, HCV dominance seems to result in a higher APRI & FIB-4 score compared to the patient having HBV dominance.

Key Clinical Message

HCV infected patients must always be screened for HBV using triple markers: HbsAg, Anti HBc antibody & Anti HBs antibody. HBV HCV co-infections patients have a higher risk of hepatocellular carcinoma hence both hepatotropic viruses need to be treated. Unfortunately, many patients in India are incidental findings.

Declarations

Ethics approval & consent to participate: The study was conducted according to the Helsinki Declaration. Participants gave an informed consent. Ethical approval was obtained from the Institute's ethics committee (Certificate reference number: AIIMS/IEC/2022/4209).

Competing Interests

None

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Nil

Availability of Data & Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author's Contribution

SC data curation, analysis & interpretation
RG: Data interpretation
DK: Data analysis
AA: Data interpretation

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