Visceral leishmaniasis-hepatitis B/C coinfections: a rising necessity to triage patients for treatment

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BACKGROUND AND OBJECTIVES: Visceral leishmaniasis (VL) is a life-threatening infection caused by Leishmania species. In Sudan, VL is caused by L. donovani. Most drugs used to treat VL, especially pentavalent antimony compounds (sodium stibogluconate, SSG), are potentially hepatotoxic. A number of fatal catastrophes happened because patients with VL-hepatitis B/C coinfection were indiscriminately treated with SSG in settings where VL and viral hepatitis coexist. This study aimed to study biochemical and hematological parameters of patients with VL-hepatitis B/C coinfections with the aim to modify treatment protocols to reduce coinfection-added morbidity and mortality.

DESIGN AND SETTINGS: This was a prospective analytical, hospital-based, and case-controlled study. The study was done at Kassab Hospital and Professor Elhassan Centre for tropical medicine during the period of February 2008 to April 2013.

MATERIALS AND METHODS: Following informed consent by the participants, 78 parasitologically confirmed VL patients with either hepatitis B or C or both and 528 sex- and age-unmatched VL patients without hepatitis B/C coinfection (control group) were enrolled sequentially. Diagnosis of hepatitis B or C was made using immunochromatographic test kits and confirmed by an enzyme-linked immunosorbent assay.

RESULTS: VL patients with hepatitis B/C coinfections had significantly increased levels of AST, ALT, and total bilirubin compared to the control group (P=0.0001 for all), with significantly decreased levels of albumin and platelets counts (P=0.0029 for both).

CONCLUSION: VL-hepatitis B/C coinfections are an emerging entity that needs anti-leishmanial treatment modification. Alternative treatments like paromomycin and amphotericin B (AmBisome) could be reserved for these patients.
countries, being highest in several African and Eastern Mediterranean countries. They represent common causes of a wide spectrum of liver diseases ranging from acute (including fulminant hepatic failure) to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Acute HBV and HCV infections can be either asymptomatic or present with symptomatic acute hepatitis. Extrahepatic manifestations of HBV infection are rare whereas HCV infection is more frequent, and both HBV and HCV infections can be difficult to diagnose and manage.

Wide interindividual variation in the natural history of both acute and chronic hepatitis B/C exists, which is explained by a combination of various host, viral, and environmental factors.

Sudan is classified among the countries with high HBV seroprevalence and exposure to the virus varied from 47% to 78%, with a hepatitis B surface antigen (HBsAg) prevalence ranging from 6.8% in central Sudan to 26% in southern Sudan. Studies of HCV showed a low seroprevalence of 2.2% to 4.8%.

VL-hepatitis B/C coinfection is an emerging entity with a cumulative effect on the liver in areas where both conditions coexist. Hepatic involvement because of either leishmaniasis or coexisting viral infection sometimes poses a dilemma in diagnosis and management.

A number of fatal catastrophes happened at our settings when patients with VL-hepatitis B/C coinfection were treated with SSG. This study was conducted to analyze biochemical and hematological profiles of patients with VL-hepatitis B/C coinfections aiming to modify treatment modalities to reduce morbidity and mortality.

MATERIALS AND METHODS

Study design

This was a prospective, analytical, hospital-based, and case-controlled study. Following informed consent, 78 parasitologically confirmed VL patients with either hepatitis B or C or both and 528 sex- and age-unmatched VL patients without hepatitis B/C coinfection (control group) were enrolled sequentially, who presented to Kassab Rural Hospital and Professor ELHassan’s Centre for Tropical Medicine, Gedarif State.

Reference hematological and biochemical values for African population were based on the report of Karita and colleagues as follows: hemoglobin in males 12.2–17.7 g/dL, hemoglobin in females 9.5–15.8 g/dL, platelets count (126–438) ×10^12 cells/µL, aspartate aminotransferase (AST) 14–60 IU/L, alanine aminotransferase (ALT) 8–61 IU/L, total bilirubin 2.9–37.0 µmol/L, and total albumin 35–52 g/L.

Clinical data and samples

Study VL patients consented to lymph node/bone marrow aspiration and hepatitis screening (HBV, HCV). Pretreatment blood samples were collected for hematologic and chemical assessment (AST, ALT, total bilirubin and albumin).

Diagnosis of hepatitis B or C was done using immunochromatographic test kits and confirmed by an enzyme-linked immunosorbent assay.

HBV infection in this situation was defined as patients with HBsAg positivity that was confirmed by molecular techniques, and HCV infection defined as anti-HCV antibody positivity that was confirmed by molecular techniques.

Data were analyzed using IBM SPSS, version 20 (The International Business Machines Corporation [IBM], USA). Results were expressed as mean (standard deviation). The Significance of difference between 2 mean values among cases and controls were determined by Student independent t test with P<.05 considered significant.

RESULTS

The mean age of VL patients with hepatitis B/C coinfections was 16.5 (9.8) years with a male-to-female ratio of 2.9, while the mean age of VL patients without hepatitis B/C coinfection was 15.0 (9.7) years (P=.2) and a male-to-female ratio of 1.68.

About two thirds (52/78; 66.7%) of the 78 VL-hepatitis B/C–coinfected patients had hepatitis B, with 1 patient having HIV in addition. A total of 27% (21/78; 26.9%) had hepatitis C, with 1 patient having HIV also. Five patients (5/78; 6.4%) had both hepatitis B and C.

ALT levels among VL-hepatitis B/C coinfections ranged from 6 to 371 IU/L with a mean concentration of 90.4 (94.1) IU/L compared to 19.8 (12.7) IU/L in the control group (P=.0001). More than half (52.5%) of VL-hepatitis B/C–coinfected patients had normal levels of ALT (8–61 IU/L) with 45% having high levels (>61 IU/L) and 2.5% showing low levels (<8 IU/L). The mean AST level was 143.6 (115.8) IU/L compared to 25.5 (18.1) IU/L in the control group (P=.0001). More than half (52.5%) of VL-hepatitis B/C–coinfected patients had normal levels of ALT (8–61 IU/L) with 45% having high levels (>61 IU/L) and 2.5% showing low levels (<8 IU/L). The mean AST level was 143.6 (115.8) IU/L compared to 25.5 (18.1) IU/L in the control group (P=.0001). Most (71%) of VL-hepatitis B/C–coinfected patients had high levels of AST (>60 IU/L) with 29% showing normal levels (14–60 IU/L). The mean total bilirubin concentration among VL-hepatitis B/C–coinfected patients was 1.1 (1.0) mg/dL compared to 0.5 (0.4) mg/dL in the control group.
(\(P=.0001\)). The mean albumin concentration among VL-hepatitis B/C–coinfected patients was 2.6 (0.7) g/dL compared to 3.0 (0.7) g/dL in the control group (\(P=.003\)).

The mean platelet count among VL-hepatitis B/C coinfections was 105×10^3 (68×10^3)/µL compared to (147×10^3 [99×10^3])/µL in the control group (\(P=.003\)). The mean hemoglobin concentration was comparable in the 2 groups with a mean of 75 (20) g/L among VL-hepatitis B/C coinfections and a mean of 82 (41) g/L in the control group (\(P=.2\)).

**DISCUSSION**

The increased male preponderance (3× females) in VL-hepatitis B/C coinfection can be partly explained by increased male preponderance in VL patients in general. VL-hepatitis B/C coinfection appears to be affecting young age groups, which is partly expected because VL is mainly a disease of children in Sudan. Alternatively, this may reflect a widespread reuse of needles in primary health care settings because in India hepatitis B and C viral infections were found to be significantly more prevalent in those who received multiple injections specially through the shared use of unsterile injection needles.21

VL-hepatitis B coinfection was more prevalent than VL-hepatitis C infection, which simply reflects the national situation of increased hepatitis B.

A considerable number of VL-hepatitis B/C coinfection (45.0%) had high ALT levels, probably indicating ongoing hepatic damage, while a minority (2.5%) had low ALT levels probably indicating a reduced liver function reserve. The reduced serum albumin levels could further point to affected liver productive function. These groups of coinfected patients certainly need treatment modification, using drugs like liposomal amphotericin B. However, the high percentage of VL-hepatitis B/C patients with high AST could point to the ongoing hepatic damage mentioned above. Alternatively, AST could be fortuitously raised as a result of mild hemolysis.22,23

Reduced platelet count in VL-hepatitis B/C coinfection could be because of the effects of megakaryocytes rather than a pan bone marrow depression, as evidenced by the comparable hemoglobin concentrations in the study groups.

In conclusion, VL-hepatitis B/C coinfection is an emerging entity that needs anti-leishmanial treatment modification. Care should be taken with the use of SSG. Biochemical parameters can help triaging VL patients to the appropriate treatment regimen.

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