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Original Article

Virologic and histologic characterisation of dual hepatitis B and C co-infection in Egyptian patients

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ABSTRACT

Background and study aims: Data about dual hepatitis C (HCV) and B (HBV) co-infection are still scarce, especially in endemic areas such as Egypt. Therefore, we aimed to characterise the virologic and histologic pattern of dual B/C co-infection in a tertiary care centre in Egypt.

Patients and methods: After obtaining approval from the review board, a retrospective design to evaluate the data registry between January 2009 and December 2012 of patients with dual HCV and HBV seropositivity (BC-group) at the Viral Hepatitis Unit in Ministry of Health and Assiut University Hospital, Egypt was conducted. Data for hepatitis B e antigen (HBe-Ag) and anti-HB core status, anti-hepatitis delta virus (anti-HDV), HBV-DNA and HCV-RNA assays and liver biopsy (METAVIR scoring) results were collected. Two other matched groups of mono-HCV (C-group) and HBV (B-group) were selected as controls. All patients were naive for antiviral therapy.

Results: A total of 3300 patients were enrolled. Dual infection was observed in 25 (0.7%) patients (all males, mean = 35.2 ± 10.2 years). Four patients (16%) were HBe-Ag-positive. Six (24%) patients were HBV-DNA-negative and all were positive for HCV RNA. Between groups, raised alanine aminotransferase (ALT) was found in 76%, 41.7% and 49.2% of the BC, B and C groups, respectively ($p = 0.023$). HBV DNA >2000 IU ml^{-1} was more in the B-group than in the BC-group (63.9% vs. 36%; $p = 0.042$) and HCV RNA >800,000 IU ml^{-1} was more in the BC-group than in the C-group (28% vs. 12.3%; $p = 0.009$). Histologically, there is no statistical significant difference between the three groups.

Conclusion: Dual hepatitis B/C infection is not uncommon and their virologic and histologic profile is modest. Further evaluation with regard to treatment and long-term follow-up is warranted.

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are important, global health problems with a peculiar concern in Egypt due to their year-by-year increasing burden [1]. Because of their shared modes of transmission, co-infection is thought to be frequent in occurrence, particularly in endemic areas [2]. However, the real impact of dual, combined HCV and HBV infection remains unelucidated, and which virus superimposes and has the upper hand remains unclear. Studies in this context are still scarce, and in areas with high endimicity, such as Egypt, a special need for more studies was warranted to further characterise the real burden of this disease and to tailor the proper targets for the treatment.

Moreover, the exact worldwide prevalence of HBV/HCV co-infection is also unknown and it might be underestimated with the phenomenon of silent (occult) HBV infection; however, dual infection with HBV and HCV in the same host ranges widely from 1% to 15% from study to study [3–5]. It has been suggested that the actual prevalence of dual infection is much higher in regions where HBV is moderately to highly endemic, as recent studies demonstrated HBV DNA in serum and/or liver tissue in a large proportion of patients with chronic HCV and even in those who are hepatitis B surface antigen (HBs-Ag)-negative which reflects a hidden iceberg phenomenon [3,6]. In addition, the literature contains conflicting data on the histologic picture of dual infection. Some studies, on the one hand, reported that dual infection leads to a more severe histological picture and more rapid progression to cirrhosis [4,7,8]; on the other hand, others do not support these findings [9,10].

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; HBs-Ag, hepatitis B-surface antigen; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; PCR, polymerase chain reaction.

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Therefore, we aimed to characterise the virologic and histologic pattern of HBV/HCV co-infection and to delineate whether it has an impact that differs from mono-infection in an Egyptian tertiary care setting.

Patients and methods

Patients

After obtaining the approval of our Local Ethics Committee, and in concordance with the Helsinki II declaration, a hospital-based, retrospective, descriptive study was conducted to evaluate the data registry of the Viral Hepatitis Management Unit in both the Assiut University Hospital outpatient clinic and Ministry of Health Hospitals, Assiut, Egypt, during the period between January 2009 and December 2012. Patients who had dual positivity for HBs-Ag and hepatitis C virus antibody (HCV-Ab) were considered chronic hepatitis B/C co-infected (BC-group). Data on hepatitis B e antigen (HBe-Ag) status, anti-hepatitis delta virus (anti-HDV), anti-HBV core (HBc-Ab), quantitative HBV-DNA polymerase chain reaction (HBV-DNA-PCR) and HCV-RNA-PCR assays, serum alanine aminotransferase (ALT) and liver biopsy (METAVIR scoring system) results were studied. All patients were naive for antiviral treatment. Informed consent was obtained from all patients.

None of the patients had any other obvious cause of hepatitis (other viruses, autoimmune disease, drug hypersensitivity, haemochromatosis, Wilson's disease or alpha-antitrypsin deficiency). None of them were alcoholic. All patients were anti-HDV-negative and anti-human immunodeficiency virus (anti-HIV)-negative.

For comparative purposes, two other matched groups of mono-infection were selected as control groups: 36 cases positive only for HBs-Ag (B-group) and another 65 cases positive only for HCV-Ab (C-group).

Serum markers for HBV and HCV infection

Serum HBs-Ag, anti-HBs, HBc-Ab, HBe-Ag, anti-HBe and anti-HDV levels were evaluated by commercially available radioimmunoassays or enzyme-linked immunosorbent assay (ELISA) kits (Abbott Diagnostics, North Chicago, IL, USA). Anti-HCV was studied using two third-generation ELISA tests (Ortho Diagnostics, Raritan, NJ, USA; and Abbott Diagnostics, North Chicago, IL, USA).

HBV DNA

Quantitative assessment of serum HBV DNA was evaluated (IU ml^{-1}) using a real-time PCR assay. According to the European Association for the Study of the Liver (EASL) for hepatitis B management guidelines 2012 [11], we categorised the HBV-DNA level into three groups: negative, <2000 IU ml^{-1} and >2000 IU ml^{-1}, which defined 2000 IU ml^{-1} as a cut-off point for treatment consideration.

HCV RNA

Quantitative assessment of serum HCV RNA was studied by a real-time PCR assay. Likewise, in concordance with the EASL for hepatitis C management guidelines 2011 [12], which defined a cut-off <800,000 IU ml^{-1} viral load as a good predictor for pre-treatment response, we categorised the HCV-RNA level into four groups: negative PCR, <100,000 IU ml^{-1}, between 100,000 and 800,000 IU ml^{-1} and >800,000 IU ml^{-1}.

Histopathology

Liver biopsy specimens were obtained from all patients included in the study. Hepatic histopathological findings were interpreted independently of clinical and biochemical data by a pathologist, according to the criteria described by the METAVIR score [13].

Data management and statistical analysis

Frequencies, percentages and means were used, as appropriate, for descriptive analysis. The analysis of variance (ANOVA) test was used to compare parametric quantitative data between groups, and the chi-squared test was used to compare parametric qualitative data; while the Mann–Whitney test was used to compare non-parametric qualitative data and Fisher's exact test used in the compression of non-parametric qualitative data. All statistical analyses were conducted using SPSS (V.16, SPSS Inc.; Chicago, IL, USA). A p value <0.05 was considered significant.

Results

Patient characteristics

During the study period, a total of 3300 patients were enrolled in our data registry. Mono-C infection was detected in 2500 (75.7%) patients (600 female, age 18–60 years), mono-B infection was detected in 800 (24.2%) patients (30 female, age 26–52 years) and dual B/C co-infection (BC-group) was detected in 25 (0.7%) patients (all male, age 21–52, mean age = 35.2 ± 10.2 years).

BC-group characteristics

The ALT pattern was normal, raised less than twofold and raised more than twofold in 24% (n = 6), 68% (n = 17) and 8% (n = 2) of patients, respectively. Only four patients (16%) were HBe-Ag-positive. HBV-DNA PCR was negative in six (24%) patients and all were positive for HCV-RNA-PCR assays, and hence, we considered HCV infection the 'dominant infection'.

The METAVIR histologic scoring ranged as follows: A1 (n = 17; 68%), A2 (n = 7; 28%) and A3 (n = 1; 4%); and with regard to the fibrosis stages, it was F1 (n = 18; 72%), F2 (n = 5; 20%) and F3 (n = 2; 8%). None of them were A0F0 or more than A3F3. The detailed description of the BC-group is shown in Table 1.

Examining the laboratory and histopathological findings between HBV-DNA-positive and -negative patients within the combined BC-group revealed no significant difference between the mean levels of HCV-RNA viral load, while there was a significant difference in histopathological changes and the ALT pattern.

Comparing the difference between HBe-Ag-positive patients versus HBe-Ag-negative patients within the combined BC-group yielded no significant difference with regard to the level of HCV RNA by the PCR assay, while there was also a significant difference with regard to the histopathological changes and the ALT pattern.

Comparison between groups

Table 2 shows a comparison of different basic variables between groups. Age and sex are matched in the three groups with no statistical difference between them. As regards the HBe-Ag status, it was found to be more in the B-group alone than in the combined BC-group (p = 0.001). In addition, the raised ALT level was found to be more in the combined BC-group than in the B and C groups (76%, 41.7% and 49.2%, respectively; p = 0.023).