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Clinical, Laboratory, and Virological Profiles of Patients with Hepatitis C and B Co-infection in Upper Egypt

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A B S T R A C T

HCV/HBV co-infection most frequently occurs in specific high-risk populations. The present study was aimed to determine the Clinical, laboratory and virological characteristics of patients with hepatitis C and B co-infection. This study included 72 patients with positive both hepatitis B surface antigen (HBs Ag) and HCV Abs. Clinical data, laboratory and imaging data were collected. Quantitative HBV-DNA polymerase chain reaction (HBV-DNA-PCR) and HCV-RNA-PCR assays results were studied. For comparative purposes, two matched groups of mono-infection were included as control groups. Liver cirrhosis was found in 30.6% of patients with chronic hepatitis C and B virus co-infection, but only in 3.7% of patients with chronic hepatitis C virus infection and 5% of patients with chronic hepatitis B virus infection. Hepatocellular carcinoma was found in 13.9% of patients with chronic hepatitis C and B virus co-infection, and only in 2.5% of patients with chronic hepatitis B virus infection.HCV PCR was positive in 75% of patients with chronic hepatitis C and B virus co-infection and in 93.7% of patients with chronic hepatitis C alone, while HBV PCR was positive in only 4.2% of patients with chronic hepatitis C and B virus co-infection and in 73.7% of patients with chronic hepatitis B alone.

Introduction

The globally high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV), in association with the shared routes of transmission of these viruses, explains the inevitable common finding of HBV/HCV co-infection. Such interactions were first described when HCV infection was known as non-A, non-B hepatitis (Lee *et al.*, 1985). It is difficult to accurately determine the number of HBV/HCV co infected individuals and there is considerable geographical variation; it is estimated that 3–22% of chronic HBV infected patients are HCV antibody positive and that 2–10% of anti-HCV-positive patients are HBs Ag positive (Chu and Lee,2008). Outside endemic areas, HBV/HCV co-infection most frequently occurs in specific high-risk

populations, particularly intravenous drug users, HIV-positive individuals and patients on hemodialysis (Chu and Lee, 2008).

Reports of occult HBV infection (HBs Ag negative, HBV DNA positive) suggest it is likely we underestimate the true prevalence of co-infection and implies that co-infection should be actively sought by HBV DNA testing, particularly in anti-HBc Ab-positive individuals (Chu and Lee, 2008; Cacciola *et al.,* 1999). From both the biological and clinical points of view, a crucial question is whether HBV and HCV may interfere in the life cycle of each other in cases of co-infection. In vitro studies performed since the early 90s had clearly demonstrated that the HCV "core" protein strongly inhibits HBV replication (Shih *et al.,* 1993; Shih *et al.,* 1995; Schüttler *et al.*, 2002; Chen *et al.,* 2003). From the virological point of view, studies showed that both HBV and HCV could interact with each other and possibly affect host immune responses (Gordon and Sherman, 2009).

Dual viral infection may occur rarely by simultaneous acute infection with both viruses or more commonly by a second acute infection in an individual already chronically infected with one hepatitis virus (superinfection). Typically, particularly in areas with high HBV prevalence, acute HCV will be superimposed on chronic HBV (Crockett, *et al.,* 2005). Acute superinfection may provoke a fulminant hepatitis (Wu *et al.*, 1994), or may lead to a chronic dual hepatitis with sequelae including cirrhosis and hepatocellular carcinoma (HCC). Rarely, superinfection with HCV may result in clearance of HBV (Sheen *et al.,* 1992). Despite the relatively large disease burden, knowledge regarding the virological interactions, clinical consequences of co-infection and optimum therapy remains incomplete.

The aims of the current study were:

Description of clinical, laboratory, and virological profiles of patients with chronic hepatitis C and B virus co-infection.

Comparing clinical, laboratory, and virological profiles of patients with chronic hepatitis C and B virus co-infection with those of patients with either chronic (HCV) infection or chronic (HBV) infection alone.

Patients and Methods

This is a hospital based; descriptive, retrospective analytic study which was conducted to evaluate the data registry of the Viral Hepatitis outpatient clinic in both the Assiut University Hospital and Sohag University Hospital, Egypt, during the period between January 2014 and March 2016. Patients who had dual positivity for HBs-Ag and hepatitis C virus antibody (HCV-Ab) were considered chronic hepatitis B&C co-infected (HCV & HBV group).

The study included 72 patients with chronic hepatitis C and B virus co-infection. All patients were naive for antiviral treatment. Demographic, possible risk factors, clinical data were collected. Laboratory and imaging data were collected. Data on hepatitis B e antigen (HBe-Ag) status, quantitative HBV-DNA polymerase chain reaction (HBV-DNA-PCR) and HCV-RNA-PCR assays results were studied.

For comparative purposes, two other matched groups of mono-infection were included as control groups: 80 cases positive only for HCV-Ab (HCV-group) and 80 cases positive only for HBs-Ag (HBV-group).

Exclusion Criteria

Identifiable other causes of chronic liver diseases (autoimmune disease, drug hypersensitivity, hemochromatosis, Wilson's disease, alpha-antitrypsin deficiency or alcohol abuse) and patients with history of antiviral therapy.

Serum Markers for HBV and HCV Infection

Serum HBs-Ag was evaluated by commercially available radio-immunoassays or enzyme-linked immunosorbent assay (ELISA) kits (Abbott Diagnostics, North Chicago, IL, USA). Anti-HCV was studied using third-generation ELISA tests (Ortho Diagnostics, Raritan, NJ, USA; and Abbott Diagnostics, North Chicago, IL, USA).

HBV DNA and HCV RNA

Quantitative assessment of serum HBV DNA and HCV RNA were studied by a real-time PCR assay.

Ethical Considerations

The study was approved by the Faculty of Medicine Ethical Committee, Assuit University. Informed consent was obtained from all patients.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS- version 17). All data was expressed as mean ± SD or frequencies. Continuous variables were compared through Student's t test and proportions were compared with chi-square tests. Results were presented as mean ± standard deviation (SD). P values of less than 0.05 were considered significant.

Results and Discussion

The study included 72 patients with chronic hepatitis C and B virus co-infection, of whom 90.3% were male. Their median age was 33 years (mean 38±11.2 years). Two other groups of mono-infection were included as control groups: 80 cases positive only for HCV-Ab (HCV-group) and 80 cases positive only for HBs-Ag (HBV-group).

All patients were native residents of Egypt. Chronic hepatitis C and B virus co-infection was significantly higher in male than female gender in comparison with other groups.

The possible risk factors for infection in all groups are summarized in Table 1.

There was no significant difference between the three groups regarding clinical characteristics except for jaundice and ascites which were significantly higher in the co-infection group (18.1% and 13.9%, respectively), as shown in Table 2.

As regards imaging results, normal liver was found in 68.1% of patients with chronic hepatitis C and B virus co-infection, 93.7% of patients with chronic hepatitis C virus infection, and in 91.3% of patients with chronic hepatitis B virus infection. Coarse liver was found in 9.7% of patients with chronic hepatitis C and B virus co-infection, 6.2% of patients with chronic hepatitis C virus infection, and in 7.5% of patients with chronic hepatitis B virus infection. Hepatomegaly was found in 22.2% of patients with chronic hepatitis C and B virus co-infection, 18.8% of patients with chronic hepatitis C virus infection, and in 21.3% of patients with chronic hepatitis B virus infection. Splenomegaly was found in 13.9% of patients with chronic hepatitis C and B virus co-infection, 11.3% of patients

with chronic hepatitis C virus infection, and in 12.5% of patients with chronic hepatitis B virus infection. Liver cirrhosis was found in 30.6% of patients with chronic hepatitis C and B virus co-infection, but only in 3.7% of patients with chronic hepatitis C virus infection and 5% of patients with chronic hepatitis B virus infection. Hepatocellular carcinoma was found in 13.9% of patients with chronic hepatitis C and B virus co-infection, and only in 2.5% of patients with chronic hepatitis B virus infection. Liver cirrhosis and hepatocellular carcinoma were significantly higher in the co-infection group.

As regards laboratory data, elevated ALT more than three-folds was found in 13.9% of patients with chronic hepatitis C and B virus co-infection, 7.5% of patients with chronic hepatitis C virus infection, and in 8.7% of patients with chronic hepatitis B virus infection. Elevated AST more than three-folds was found in 15.3% of patients with chronic hepatitis C and B virus co-infection, 8.7% of patients with chronic hepatitis C virus infection, and in 8.7% of patients with chronic hepatitis B virus infection. Reduced serum albumin was found in 29.2% of patients with chronic hepatitis C and B virus co-infection, 3.7% of patients with chronic hepatitis C virus infection, and in 5% of patients with chronic hepatitis B virus infection. Low platelet count was found in 45.8% of patients with chronic hepatitis C and B virus co-infection, but only in 12.5% of patients with chronic hepatitis C virus infection and 15% of patients with chronic hepatitis B virus infection.

Reduced serum albumin and low platelet count were significantly higher in the co-infection group, as shown in Table 3.

Both HCV and HBV PCR were positive in 12.9% of patients with chronic hepatitis C and B virus co-infection and both of them were negative in 8.4% of those patients.

HCV PCR was positive in 75% of patients with chronic hepatitis C and B virus co-infection and in 93.7% of patients with chronic hepatitis C alone, while HBV PCR was positive in only 4.2% of patients with chronic hepatitis C and B virus co-infection and in 73.7% of patients with chronic hepatitis B alone.

By comparing the HCV viral load between the co-infection group and the C group, the viral load was significantly more in the co-infection group than in the C group.

However, when comparing the HBV viral load between the co-infection group and the B group, the contrast was noted. The HBV viral load was significantly more in the B group than the co-infection group, as shown in Table 4.

Our study disclosed some important observations. First, chronic hepatitis C and B virus co-infection had higher prevalence in male than female gender in comparison with the solely chronic hepatitis C or B virus infection. However, the possible risk factors for infection as dental manipulations, surgical operations, previous blood transfusion, infection in the family, and tattooing were the same for all groups.

Second, arthralgia, fatigue, and abdominal pain were the main clinical manifestations of all groups. There was no major difference between the three groups regarding clinical characteristics except for jaundice and ascites which were higher in the co-infection group. Third, most of the patients in the mono-infection groups had normal liver on ultrasonographic examination and normal liver function tests. Development of liver cirrhosis and hepatocellular carcinoma was

higher in the co-infection group. Fourth, demonstrate a dominant role of HCV in patients with dual HBV–HCV infection. Fifth, the HCV viral load was more in the co-infection group than in the C group. However, the HBV viral load was more in the B group than the co-infection group.

The results of this study are similar to a previous study by Tyson *et al.,* (2013), who estimated the prevalence and the predictors of HBV co-infection in a US cohort of HCV-infected patients. They reported that independent associations with HBV co-infection compared with HCV mono-infection were age ≤50 years, male sex, positive HIV status, resident in the south of the country, light alcohol use, lower education level, history of hemophilia, sickle cell anemia or thalassemia, history of blood transfusion, cocaine and other drug use.

Also studies that were done by Deterding *et al.,* (2009), Bhasin *et al.,* (2012) and Maida *et al.,* (2008) reported that HBV shares common modes of transmission with HCV. Blood, body fluids containing visible blood, semen, and vaginal secretions represent a risk of transmission. Both infections are transmitted by percutaneous and mucosal exposure to infective blood or body fluids. The main modes of HBV and/or HCV transmission include sexual or close household contact with an infected person, perinatal mother to infant transmission, injecting drug use, and nosocomial exposure. They reported that HBV and/or HCV can be transmitted by transfusion of infected blood or blood products, sharing unsterilized needles for intravenous drug use, hemodialysis, acupuncture, tattooing, and injuries from contaminated sharp instruments. Maida, *et al.,* (2008) mentioned that the risk factors of dual infection are similar to those of single infection of the two viruses.

Our present study bears some similarities with previous reports by Caccamo, *et al.,* (2014) and Cardoso, *et al.,* (2013), who found that the clinical pattern of the chronic HBV/HCV co-infection is indistinguishable from that of a chronic mono-infection. It includes fatigue, vague abdominal discomfort, nausea and vomiting, anorexia, sometimes arthralgia and rash, followed by bleeding gums. This observation can be explained by the fact that dual infection with HBV and HCV leads to mutual suppression of both viruses (Liu and Hou, 2006). However, several studies have suggested that multiple HBV and HCV infection may be associated with more severe clinical presentation (Fattovich, 1991 & Crespo *et al.,* 1994). A Saudi Arabia study showed that the patients with dual HCV and HBV infection had more decompensated liver disease (Mohammed, *et al.,* 1997).

In the present study, our results also showed that the majority of patients in the mono-infection groups had normal liver on ultrasonographic examination and normal liver function tests. Development of liver cirrhosis and hepatocellular carcinoma was higher in the co-infection group. Indeed, several cross-sectional studies found that co-infection is associated with a higher prevalence of liver cirrhosis and hepatic decompensation as compared with HBV or HCV mono-infection (Zarski *et al.,* 1998; Donato *et al.,* 1998).

Moreover, co-infection has been associated with increased risk of progression of the liver fibrosis and the establishment of cirrhosis (Mohammed *et al.,* 1997; European Association For The Study Of The Liver, 2012) and is an independent predictor of HCC development (Huang *et al.,* 2011; Italian Association for the Study of the Liver, 2010; Aghemo *et al.,* 2014; Weltman *et al.,* 1995).

Table.1 Demographic characteristics and history of patients in all groups

Characteristics	B&C group n (%) (n =72)	HCV group n (%) (n =80)	HBV group n (%) (n =80)	p-value
Male gender	65(90.3%)	52(65%)	61(76.3%)	0.021*
Age (Mean ± SD)	38±11.2	41±13.2	33±12.7	0.542
Residence				
Urban	27(37.5%)	26(32.5%)	29(36.3%)	0.332
Rural	45(62.5%)	54(67.5%)	51(63.7%)	0.247
Smoking	43(59.7%)	44(55%)	41(51.3%)	0.534
Past history:				
Hepatitis	9(12.5%)	9(11.3%)	8(10%)	0.265
Blood transfusion	10(13.9%)	9(11.3%)	7(8.8%)	0.064
Surgical operations	25(34.7%)	21(26.3%)	15(18.8%)	0.073
Dental manipulations	54(75%)	62(77.5%)	59 (73.8%)	0.413
Parenteral drug abuse	3(4.2%)	4(5%)	5(6.3%)	0.327
Tattooing	6(8.3%)	5(6.3%)	7(8.8%)	0.422
Schistosomiasis	8(11.1%)	8(10%)	7(8.8%)	0.328
Family history of liver disease	10(13.9%)	9(11.3%)	11(13.8%)	0.265

* Statistically significant

Table.2 Clinical characteristics of patients in all groups

Characteristics	B&C group n (%) (n =72)	HCV group n (%) (n =80)	HBV group n (%) (n =80)	p-value
Fatigue	50(69.4 %)	40(50%)	41(51.3%)	0.217
Abdominal pain	31(43%)	33(41.3%)	30(37.5%)	0.341
Arthralgia	43(59.7%)	41(51.3%)	38(47.5%)	0.513
Hemorrhage: Gums	3(4.2%)	1(1.3%)	2(2.6%)	0.624
Nose	2(2.8%)	1(1.3%)	0(0%)	0.078
Abdominal distension	12(16.7%)	10(12.5%)	8(10%)	0.216
Loss of libido	7(9.7%)	6(7.5%)	5(6.3%)	0.363
Jaundice	13(18.1%)	3(3.8%)	4(5%)	0.011*
Hepatomegaly	16(22.2%)	15(18.8%)	17(21.3%)	0.079
Splenomegaly	10(13.9%)	9(11.3%)	10(12.5%)	0.321
Ascites	10(a)	1(1.3%)	2(2.6%)	0.021*
Spider naevi	9(12.5%)	9(11.3%)	10(12.5%)	0.421
Palmar erythema	3(4.2%)	3(3.8%)	3(3.8%)	0.301
Gynaecomastia	4(5.6%)	3(3.8%)	4(5%)	0.221
Edema of lower limbs	5(6.9%)	4(5%)	5(6.3%)	0.426
Subcutaneous hemorrhage	6(8.3%)	6(7.5%)	7(8.8%)	0.315

* Statistically significant

Table.3 Imaging and laboratory characteristics of patients in all groups

Characteristics	B&C group n (%) (n=72)	HCV group n (%) (n =80)	HBV group n (%) (n =80)	p-value
Imaging data:				
Normal liver	49(68.1%)	75(93.7%)	73(91.3%)	0.207
Coarse liver	7(9.7%)	5(6.2%)	6 (7.5%)	0.114
Hepatomegaly	16(22.2%)	15(18.8%)	17(21.3%)	0.079
Splenomegaly	10(13.9%)	9(11.3%)	10(12.5%)	0.321
Cirrhosis	22(30.6%)	3(3.7%)	4(5%)	0.011*
Ascites	12(16.7%)	2(2.5%)	3(3.7%)	0.021*
Gall bladder stones	20(27.8%)	14(17.5%)	11(13.8%)	0.067
Hepatic haemangioma	2(2.8%)	2(2.5%)	0(0%)	0.217
Portal vein dilatation	9(12.5%)	7(8.7%)	8(10%)	0.075
Hepatocellular carcinoma	10(13.9%)	0(0%)	2(2.5%)	0.004*
Laboratory data:				
ALT: Normal	50(69.4%)	67(83.7%)	65(81.2%)	0.206
Raised up to 3 folds	12(16.7%)	7(8.7%)	8(10%)	0.113
Raised > 3 folds	10(13.9%)	6(7.5%)	7(8.7%)	0.097
AST: Normal	48(66.7%)	65(81.2%)	63(78.7%)	0.317
Raised up to 3 folds	13(18.1%)	8(10%)	10(12.5%)	0.089
Raised > 3 folds	11(15.3%)	7(8.7%)	7(8.7%)	0.411
Serum total bilirubin: Normal	58(80.6%)	75(93.7%)	74(92.5%)	0.066
Raised	14(19.4%)	5(6.2%)	6(7.5%)	0.012*
Serum albumin: Normal	51(70.8%)	77(96.2%)	76(95%)	0.224
Reduced	21(29.2%)	3(3.7%)	4(5%)	0.065
Prothrombin time: Normal	55(76.4%)	76(95%)	75(93.7%)	0.097
Prolonged > 3 seconds than control	17(23.6%)	4(5%)	5(6.2%)	0.032*
Low platelet count	33(45.8%)	10(12.5%)	12(15%)	0.025*

* Statistically significant

Table.4 Virological characteristics of patients in all groups

Characteristics	B&C group n (%) (n =72)	HCV group n (%) (n =80)	HBV group n (%) (n =80)	p-value
+ ve HCV&HBV PCR	9(12.9%)	--	--	--
+ ve HCV PCR	54(75%)	75(93.7%)	--	0.045*
+ ve HBV PCR	3(4.2%)	--	59(73.7%)	0.015*
-ve HCV&HBV PCR	6(8.4%)	--	--	--
HCV-PCR (mean+SD)	1836923.23 ± 3638760.34	1524951.26 ± 2436953.22	--	0.019*
HBV-PCR (mean+SD)	1633913.15 ± 2738950.35	--	1946921.26 ± 5639960.24	0.008*

* Statistically significant
HBV: Hepatitis B virus
HCV: Hepatitis C virus
PCR: Polymerase chain reaction

There are, however, studies that do not support these conclusions (Villari *et al.,* 1995; Colombari *et al.,* 1993). In a cohort of Egyptians dually infected done by Mekky *et al.,* (2013), patients had no difference regarding the histologic score in comparison to mono-infected patients. These discrepancies can be explained by biases in the design of the studies (small sample size, type of studies as retrospective studies, community or hospital-based studies) and technical reasons (sensitivity of anti-HCV assays). On the other hand, the fact that the co-infection of HBV and HCV ends up in the dominance of either virus and the suppression of the other could partially explain the similarity in histologic findings between co-infected and mono-infected patients (Colombari *et al.,* 1993).

Many epidemiologic studies in patients with HCV and HBV co-infection have documented an increased risk of HCC confirmed by three meta-analyses (Donato *et al.,* 1998; Cho *et al.,* 2011; Shi *et al.,* 2005). Given the role of the chronic necro-inflammation and especially cirrhosis in the pathogenesis of HCC together with the higher incidence of cirrhosis and a greater degree of hepatic damage in mono-infection, a synergistic carcinogenic interaction between the two viruses is most probable. The different mechanisms that have been hypothesized as being associated with the development of HBV- or HCV-related HCC suggest that both viruses could play an active role at different steps of the carcinogenic process. Most evidence suggests that HBV is capable of initiating the neoplastic process, while HCV could act as a promoter, and that they may be synergistic in developing HCC (Shi *et al.,* 2005).

In the present study, we demonstrated that Both HCV and HBV PCR were positive in 12.9% of patients with chronic hepatitis C and B virus co-infection and both of them were negative in 8.4% of those patients. HCV PCR was positive in 75% of patients with chronic hepatitis C and B virus co-infection and in 93.7% of patients with chronic hepatitis C alone, while HBV PCR was positive in only 4.2% of patients with chronic hepatitis C and B virus co-infection and in 73.7% of patients with chronic hepatitis B alone.

The HCV viral load was more in the co-infection group than in the C group. However, the HBV viral load was more in the B group than the co-infection group.

This is in agreement with many studies in which the inhibition of HBV replication by HCV was observed (Sagnelli *et al.,* 2000; Pontisso *et al.,* 1998; Jardi *et al.,* 2001). Serum HBV DNA was found more frequently in patients with chronic hepatitis B mono-infection than in patients with chronic hepatitis C and B virus co-infection and HBV DNA levels was lower in co-infection than in mono-infection (Sagnelli *et al.,* 2000). Liaw *et al.,* (1994), reported that HCV infection might suppress HBV or even eliminate and directly interfere with HBV replication and become the sole cause of persistent hepatitis in a small number of patients. Also Shih *et al.,* (1993) found a moderate 2-4 fold reduction of HBV mRNA and HBV antigen expression in presence of HCV structure genes and a stronger suppression up to 20 fold of HBV particle secretion.

Zarski *et al.,* (1998) compared virological characteristics of patients with chronic hepatitis C and B co-infection with those of patients with chronic C alone. They found an inverse relationship between the replicative patterns of both viruses. The HCV RNA level was significantly reduced in HBV DNA positive patients compared with HBV DNA negative patients. An

Italian multicenter case-control study (Sagnelli, *et al.*, 2000), was done on a large number of patients with chronic hepatitis from a multiple hepatitis virus infection that was compared with patients with chronic hepatitis caused by a single virus. In this study, HCV RNA was detected more frequently in patients with anti-HCV positive (90.7%) than in patients with HBsAg/anti-HCV positive (65.2%, $p<0.001$).

In conclusion, Chronic hepatitis C and B virus co-infection is a complex clinical/virological entity. The risk factors of the co-infection are similar to those of single infection of the two viruses. This co-infection appears to be associated with the most severe forms of chronic liver disease and it is an important risk factor for development of liver cirrhosis and hepatocellular carcinoma. Different, often dynamic virological profiles may be found that are strictly related to the activity of one or both the viruses overtime. Thus, a careful evaluation of the HCV and HBV viremia levels is essential for a correct diagnosis, follow-up, and proper therapeutic approach.

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