INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print), 2222-5234 (Online)
http://www.innspub.net
Vol. 13, No. 3, p. 68-74, 2018

RESEARCH PAPER OPEN ACCESS

Comparison of liver function tests between different genotypes of HBV and HCV in non-responders of HBV-HCVCo-infected patients with healthy controls

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Key words: Hepatitis B, Hepatitis C, Viral infection, Viral resistant, Biochemical test, genotyping in retroviruses infected patients.

http://dx.doi.org/10.12692/ijb/13.3.68-74 Article published on September 07, 2018

Abstract

Hepatitis B and C co-infection may leads to cirrhosis resulting in hepatocellular carcinoma with poorer survival rate. Pegylated interferon and ribavirin treatment is considered as gold standard. Despite of adequate treatment, some patients remained non-responders. Due to this reason, this study was designed to compare different parameters of liver function tests along with HBV- HCV genotyping in non-responders of HBV-HCV co-infection with normal controls. Study population was divided in two groups. Group A (patient group) includes 30 HBV-HCV co-infected patients and Group B (control group).includes 30 normal individuals. Blood samples of both groups were collected. Samples were analyzed for HBV and HCV genotyping using automated kits of Abbott laboratories and Liver Functions testing (ALT, ALP, Bilirubin, Albumin) using ROCHE COBAS-501 automated system. Statistical analysis using chi-square test for ordinal data and t-test for numerical data was used using p-value <0.05 as significant. In all patients, HCV genotype was '3'. Most were co-infected with HBV genotype B (73.3%) as compared to genotype C (26.6%). Male to female ratio was about 1:1.1 in control group as compared to 6.5:1 in patients group. Mean age of controls was younger (32.3±6.8 years) as compared to patients (36.85±9.6 years).Overall, liver function tests were significantly high in patients group (p-value <0.05) as compared to controls. However, albumin and alkaline phosphatase levels show insignificant difference in HBV Genotype B and C patients. In conclusion, HBV-HCV co-infected patients have higher mean age, mean values of different parameters of liver function tests were significantly high in patient group as compared to control group.

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Introduction

Hepatitis B (HBV) and Hepatitis C (HCV) chronic infection is a worldwide problem. About 75% of the hepatitis B patients reside in Asia and western pacific and about 1.3 to 1.6% patients of HCV belongs to USA (Williams, 2006; Bini and Perumals, 2010; Crockett 2005 or Karoney and Siika, and Keeffe, 2013).Hepatitis B and C co-infection may lead to extensive necrosis, cirrhosis and hepatocellular carcinoma (HCC) (Pan *et al.*, 2007). HBV-HCV co-infection is not unusual particularly in regions where HBV and HCV infections are endemic mainly in people with parental infections (Lee *et al.*, 2007; Sagnelli *et al.*, 2009). The patients with co-infection undergo a severe liver disease course with poorer survival rate (Biliotti *et al.*, 2008).

HBV is the member of Hepa DNA viridae (group of small enveloped viruses with partially double stranded DNA). They have a limited host range (Neuveut *et al.*, 2010). HBV follows strict pattern for its geo ethnic distribution. HBV genotypes Band C are more common among East Asian countries (Datta S *et al.*, 2012).HCV belongs to the family Flaviviridae. HCV is an enveloped virus with positive stranded RNA genome (Bartosch and Cosset, 2006). Around 30 genotypes of HCV have been known (Datta *et al.*, 2012).

The rate of mortality is higher in patients with HBV-HCV co-infection. The mortality rate due to HBV is 3.2% whereas that of HCV is 5.3%. Mortality rate of HBV-HCV co-infection is even higher than that of HBV or HCV alone i.e., 7.1% (Pan *et al.*, 2007).

The increased mortality rate is because of continued drug use along with complications. HBV-HCV co-infection is responsible for hepato-carcinogenesis because HBV enhances replication of HCV and both these viruses are repeatedly isolated from liver biopsies cirrhotic and HCC patients.

Pegylated interferon along with ribavirin treatment for co-infection is considered to be the gold standard. HBV-HCV co-infection is treated with interferon α, the most studied agent. Most of the studies reported that interferon therapy has sustained biochemical response rate same as in case of chronic HCV alone.

Combined treatment of 21 HBV-HCV co-infected patients with IFN-α2b and ribavirin has proven their efficacy. Interferon along with ribavirin treatment is administered for 24/48 weeks to eliminate the infection.

The present study was planned to compare different parameters of liver function tests (LFTs) in non-responders patients with HBV-HCV co-infection and normal controls and between different genotypes of HBV infection.

Material and methods

The study population was divided in two groups

Patient Group

Control Group.

Equal numbers of individuals (thirty) were enrolled in each group.

Inclusion criteria

Patient Group: seropositive HBV-HCV co-infected patients from different gastroenterology departments of Rawalpindi/Islamabad who were declared non-responders by treating physician.

Control Group: Healthy individuals with no known history of hepatitis or jaundice and negative ELISA test for Anti-HCV antibody and HBs Ag.

Protocol of study

A written consent was obtained from each individual. Demographic data including age, gender, duration of illness and treatment, of both groups were collected. Venous blood sample (07 ml) was drawn from each individual of both groups. Samples were collected in aseptic and sterile conditions.

The following blood tests were done in all individuals

First, HBV and HCV genotyping using automated kits of Abbott laboratories.

Second, Liver Functions tests (ALT, ALP, Bilirubin and Albumin) using ROCHE COBAS-501 automated system.

Data analysis

Data was analyzed using SPSS version 17. Mean values along with standard deviations were calculated for the variables like age, gender and LFTs. Statistical comparison of different parameters of LFTs between two groups was done considering p-value of less than 0.05 as significant.

Results

The study recruited a total of sixty subjects comprising of 30 normal healthy controls (Control Group) and 30 hepatitis B and C co-infected patients (patient Group).

Table 1. Statistical Analysis of Different parameters between patients and control Group.

Independent Samples Test					
		Levene's Test for Equality of Variances		t-test for Equality of Means	
Age		F	Sig.	t	df
	Equal variances assumed	10.735	.002	3.379	58
	Equal variances not assumed			3.379	52.232
ALT levels	Equal variances assumed	20.996	.000	4.296	58
	Equal variances not assumed			4.296	30.282
Bilirubin	Equal variances assumed	3.909	.053	3.345	58
	Equal variances not assumed			3.345	46.929
ALP	Equal variances assumed	6.134	.016	3.360	58
	Equal variances not assumed			3.360	47.584
Albumin	Equal variances assumed	10.816	.002	-2.720	58
	Equal variances not assumed			-2.720	57.402

Genotyping

Regarding genotyping, HCV genotype 3 was found in all subjects of patient group whereas most were co-infected with HBV genotype B (n=22) as compared to HBV genotype C (n=8).

Gender distribution

A total of 40 males and 20 females (both groups) were included in the study. The ratio of male (n=14) to female (n=16) was about 1:1.14 among control group whereas ratio of male (n=26) to female (n=4) in patient group was 6.5:1. Eighteen of the HBV genotype B (n=22) patients were males (81.8%) whereas 4 were females (18.2%). All of the HBV genotype C (n=8) affected subjects were females (100%).

Age

The mean age of the control group was 32.33 years (SD±6.68 years) and patient group was 39.47 years (SD±9.47 years). Mean age of the HBV genotype B (n=22) affected subjects was quite younger i.e., 38.4 years (SD±10.1 years) as compared to HBV genotype C affected subjects whose mean age was 42.5 years (SD±8.7 years).

Liver Function Tests

Statistical analysis of different parameters of LFTs between patients group and control group is shown in Table 1.

Liver function tests (LFTs) values in Group A and Group B is shown in Figure 1 (ALT and ALP values) and Figure 2 (Bilirubin and albumin values). The statistical analysis showed that mean ALT levels of

patient group (66.0±44.2U/L) was significantly higher ($p<0.05$) as compared to control group (30.9±6.57 U/L). Mean ALP levels of patient group (292.4±120.8U/L) was significantly higher ($p<0.05$) as compared to control group (207.4±72.7 U/L). Mean bilirubin levels of patient group (1.6±0.8 mg/dl) was significantly higher ($p<0.05$) as compared to the control group (0.6±0.2 mg/dl). Although, mean Albumin levels of patient group (3.9±0.5 U/L) is higher as compared to control group (3.5±0.5 g/dl), but the difference was statistically insignificant ($p > 0.5$).

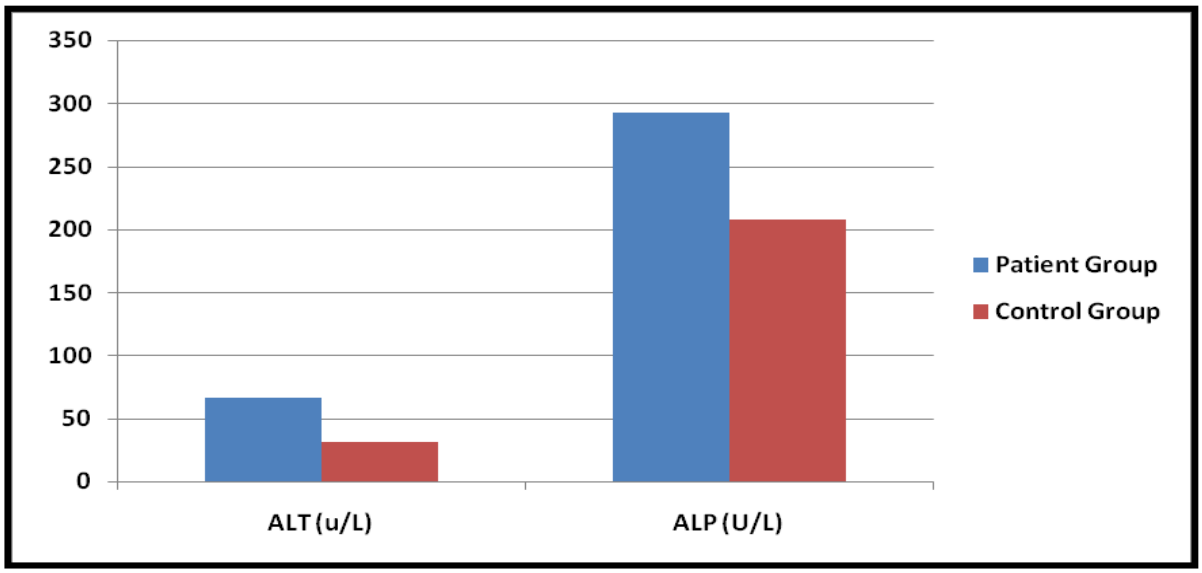

Fig. 1. Mean values of ALT and ALP in patients and control groups.

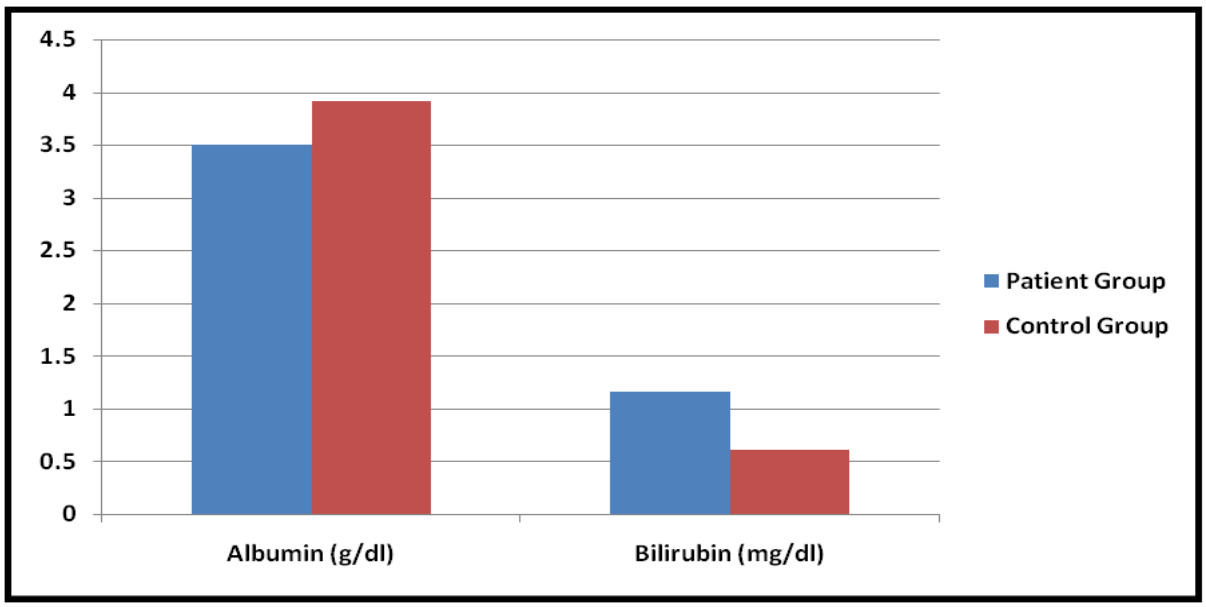

Fig. 2. Mean albumin and bilirubin values in patients and control groups.

Liver function tests (LFTs) values in HBV genotype B and HBV genotype C is shown in Figure 3 (ALT and ALP values) and Figure 4 (Bilirubin and albumin values). Statistical analysis showed that mean ALT value of HBV genotype B (n=22) affected subjects (72.3±51.3 U/L) was significantly higher ($p<0.05$) as compared to HBV genotype C (n=8) affected subjects (48.5±11.6 U/L). However, there was insignificant difference ($p=0.62$) in mean ALP values of the HBV genotype B affected subjects (291±105.8U/L) and HBV genotype C affected subjects (296.3 ±175.4 U/L). Mean bilirubin and albumin values of the HBV

genotype B affected subjects was almost equal (insignificant difference) to that of HBV genotype C affected subjects (Figure 4).

Discussion

HBV-HCV co-infection is posing serious threat and has fatal consequences to human population around the world. Numerous risk factors are linked with the spread of hepatitis B and C including unscreened blood transfusions, use of injectable drugs, wounds by barbers and reuse of disposable syringes.

Pegylated interferon along with ribavirin is being used as standard treatment for Hepatitis C (Chung *et al.*, 2004).

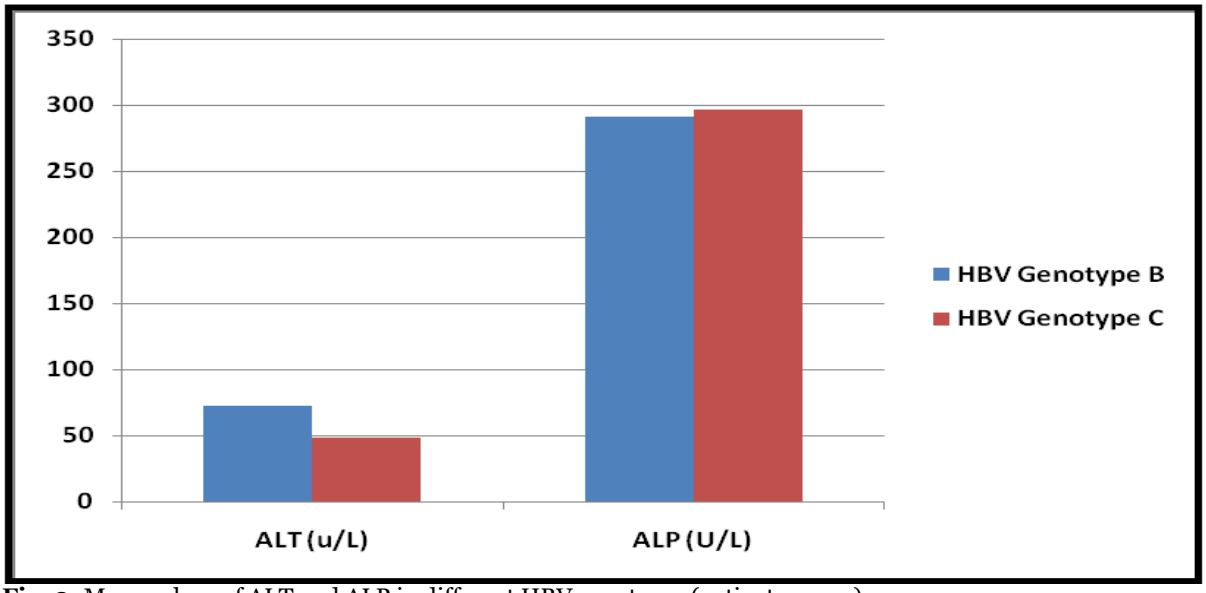

Fig. 3. Mean values of ALT and ALP in different HBV genotypes (patients group).

Interferon therapy in combination with ribavirin has improved sustained viral response (SVR) among the patients (Ahmad *et al.*, 2012). Treatment of co-infected patients depends on the predominant infection as per instructions of European association for study of liver diseases. In case both infections are active then HCV will be treated first and if HCV infection reduces during treatment and HBV infection increases then HBV treatment should be started.

Our study has showed that findings of liver function tests among HBV-HCV co-infected patients as compared to controls confirmed that mean levels of serum bilirubin, ALT and ALP are significantly higher among co-infected patients as compared to controls(p value <0.05) showing great hepatocellular damage. No significant difference was observed between different clinical findings of the HBV genotype B and C co-infected with HCV. In addition, mean age of HBV-HCV co-infected patients is higher as compared to that of normal healthy individuals indicating that HBV-HCV co-infection is more common in elders (about 40 years).

Little number of studies is available on concurrent HBV and HCV acute infection but shows that the collaboration between these two viruses is similar to that which follows in chronic infections. The co-infection is modulating the pathogenesis of one another. In some cases there have been reports that co-infected individuals have high ALT levels and histological activity. Whereas in others there lowering of ALT levels have been reported.

The facts suggest that the disease is evolving more severely among co-infected individuals. Evidence shows that the probability of evolution to HCC is higher among co-infected patients. In a prospective study conducted on 290 individuals suffering from cirrhosis showed that HBV-HCV co-infection is a

predictive factor for HCC development (Mitre and Mendonça, 2007). Because of the limited availability of acute HBV-HCV co-infected patients, only a few studies are available and not much is known about this facet (Liu and Hou, 2006). So our study will also be helpful to show the different aspects of HBV-HCV co-infection which are not covered by other studies.

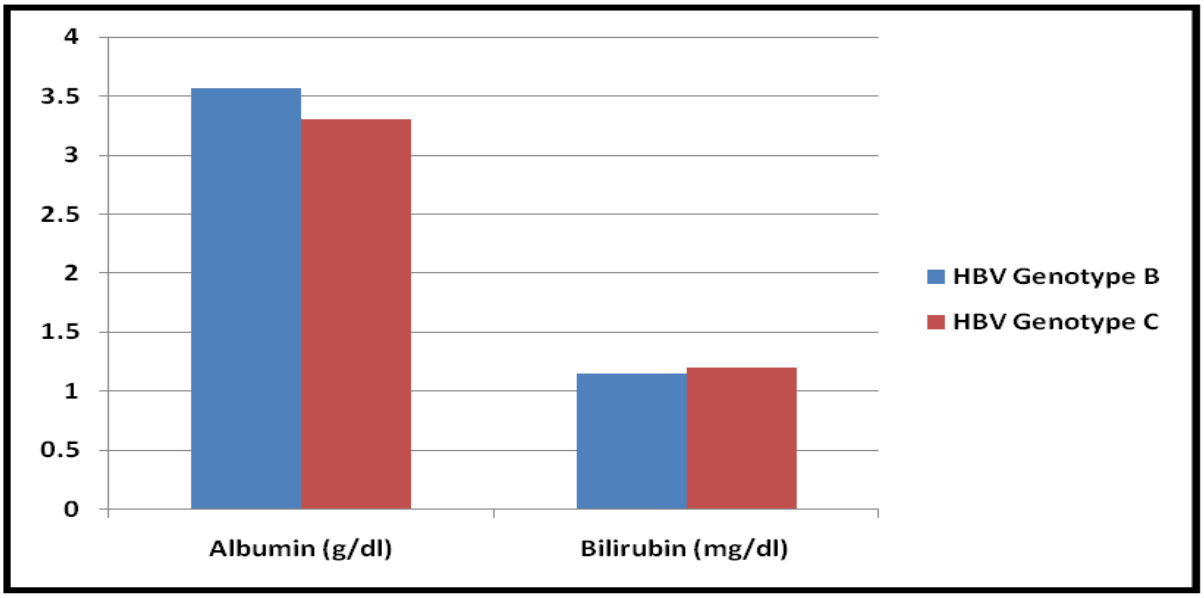

Fig. 4. Mean values of albumin and bilirubin in different HBV genotypes (patients group).

Conclusion

The study concludes that HBV-HCV co-infected subjects have higher mean age. Overall mean values of different parameters of liver function tests were significantly deregulated in patient group as compared to control group whereas albumin and alkaline phosphatase levels show insignificant difference in HBV Genotype B and Genotype C patients (in patients group).

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