Research Article

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Analysis of Virological, Histological and Clinical Features of Hepatitis Delta Virus Infection in Southeastern Turkey

Güneydoğu Anadolu Bölgesi'ndeki Delta Hepatit Virüs Enfeksiyonlu Hastalarımızın Virolojik, Histolojik ve Klinik Özelliklerinin Analizi

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ABSTRACT

Objectives: The present study aims to investigate biochemical, virological and histological characteristics of hepatitis delta virus infection, which is a serious problem in our region, as well as its relationship with chronic hepatitis B virus (HBV) infection and cirrhosis.

Materials and Methods: A total of 220 patients were included in the study. The patients were divided into three groups: group 1 included patients with hepatitis delta virus-related cirrhosis (DA cirrhosis), group 2 consisted of patients with chronic delta hepatitis (CHD) and group 3 composed of patients with chronic hepatitis B (CHB). Biochemical and virological parameters of the patients were analyzed. Patients with CHB and CHD underwent biopsy for histological examination. The results were compared among the three groups.

Results: Seventy-five (34.09%) of the patients were women, 145 (65.90%) were males and their mean age was 38.04 years. There were 44 patients (20%) with delta hepatitis-associated cirrhosis, 86 patients with CHD (39.09%) and 90 patients with CHD (40.9%). HBV DNA level was significantly lower in patients with cirrhosis and chronic delta hepatitis than in patients with CHB (p<0.001) (p<0.001). Histology activity score and fibrosis stage were significantly higher in CHD than in CHB (p<0.001) (p<0.001). A significant correlation was determined between fibrosis stage and hepatitis delta virus RNA in CHD patients. There was also a significant correlation between necroinflammatory score and alanine aminotransferase in CHD (p=0.021).

Conclusion: In Turkey, the age of onset of delta hepatitis is low and accordingly, related liver cirrhosis develops at a younger age. HBV DNA levels appear to be suppressed in patients with delta hepatitis as compared to patients with CHB. Histologically severe disease picture is seen in patients with delta hepatitis and delta hepatitis-positive cirrhotic patients.

Keywords: Hepatitis delta virus, hepatitis B virus, cirrhosis, liver biopsy

ÖZ

Amaç: Hepatitis delta virüsü replikasyonu için hepatit B yüzey antijenine ihtiyaç duyan defektif bir virüstür. Bu çalışmadaki amacımız bölgemizdeki delta hepatitli hastaların virolojik, histolojik ve biyokimyasal özelliklerini araştırmaktır.

Gereç ve Yöntemler: Toplam 220 hasta çalışmaya alındı. Hastalar üç grupta incelendi: delta hepatite bağlı siroz (Dİ siroz), kronik delta hepatit (CHD) ve kronik hepatit B (CHB). Kronik delta ve hepatit B grubundaki hastaların biyopsilerindeki histolojik özellikleri incelendi. Üç grubun özellikleri karşılaştırıldı.

Bulgular: Hastaların 75'i (%34,09) kadın, 145'i (%65,90) erkek ve ortalama yaşları 38,04 idi. Delta hepatite bağlı sirozlu 44 hasta (%20), CHD'li 86 hasta (%39,09) ve CHB'li 90 (%40,9) hasta vardı. Siroz ve kronik delta hepatitli gruplar arasında HBV DNA düzeyleri açısından anlamlı farklılık yoktu (p=0,466). Ancak bu iki grubun HBV DNA düzeyleri kronik hepatit B'li gruba göre anlamlı olarak düşüktü (p<0,001-p<0,001). CHD'nin histolojik aktivite ve fibrozis evresi CHB'den anlamlı olarak yüksekti (p<0,001) (p<0,001). CHD'deki hastaların HDV RNA değeri ile fibrozis evreleri arasında anlamlı korelasyon vardı. Bu grupta alaninamino transferaz ile histolojik aktivite arasında anlamlı korelasyon saptandı (p=0,021).

Sonuç: Türkiye'de delta hepatit başlangıç yaşı küçük olduğu için kronik karaciğer hastalığı da genç yaşta ortaya çıkar. Delta hepatit, delta ile ilişkili siroz ve hepatit B'li hastaların ALT düzeyi farklılıklar gösterir. HBV DNA seviyeleri, delta hepatitli hastalarda kronik hepatit B'li hastalarla karşılaştırıldığında baskılanmıştır. Histolojik olarak delta hepatit pozitif hastalarda daha ağır bir hastalık tablosu mevcuttur.

Anahtar Kelimeler: Hepatit delta virüs, hepatit B virüs, siroz, karaciğer biyopsisi

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Introduction

Hepatitis delta virus (HDV) is a defective RNA virus. HDV causes co-infection and super infection by using hepatitis B virus (HBV) surface antigen (HBsAg). Today, HDV infection remains a serious health problem particularly in endemic regions (1). There are more than 240 million chronic carriers of HBV, and approximately 15 million of them have serological evidence of exposure to HDV, worldwide (2,3,4).

The prevalence of HDV infection in Europe has changed with the control of HBV infection achieved in the last 20 years (5). The current prevalence of HDV infection among HBsAg carriers is approximately 10% in Italy (6) and 11% in Turkey (7). In Turkey, HDV strains exhibit wide genetic diversity reflecting an ancient evolution and/or successive outbreaks (8). However, HDV still accounts for almost one half of overall cases of liver cirrhosis and hepatocellular carcinoma in southeastern Turkey (9).

Chronic HBV and HDV infections have wide range of clinical manifestations from the state of asymptomatic carrier to chronic active hepatitis, liver cirrhosis and hepatocellular carcinoma. However, underlying mechanisms of such clinical variety have not been fully defined yet (1). In the present study, we aimed to investigate biochemical, virological and histological parameters in HDV infection, which is a serious problem in our region, and to investigate its relationship with HBV and HDV viral loads. Within this context, our aim is to designate characteristic features of HDV and it will contribute to determining the follow-up, treatment and natural course of the disease.

Materials and Methods

The study included a total of 220 patients [75 (34.09%) females and 145 (65.90%) males] aged between 15 and 70 years, who were admitted to the gastroenterology and hepatology inpatient or outpatient clinics at Dicle University Faculty of Medicine Gastroenterology and Hepatology Department and fulfilled the inclusion criteria. Physical examination findings, results of laboratory tests for biochemical, hematological and virological parameters and HBV and HDV markers, and epidemiologic history of all patients were recorded.

Study Groups and Definition

Patients were grouped into three groups:

HDV-related cirrhosis (DA cirrhosis).

Chronic hepatitis delta (CHD) without cirrhosis.

Chronic hepatitis B (CHB) (without hepatitis D).

HBsAg-positive and anti-HBs-negative patients, who had undulating alanine aminotransferase (ALT) concentrations for at least 6 months were defined as CHB patients. Liver biopsy was performed in 45 patients in CHD and in 77 patients in CHB. Histopathological findings were recorded.

The present study was retrospective.

Eligibility Criteria

Treatment-naive patients or patients who did not receive treatment for at least six months were included in the study.

The diagnosis of liver cirrhosis was established based on laboratory, histological analysis or abdominal ultrasonography findings which demonstrated hepatic surface irregularity, caudate lobe hypertrophy, splenomegaly and injury to the hepatic parenchyma, and on the presence of esophageal varices confirmed by endoscopy. The group with active CHD consisted of patients with positive HBsAg and anti-delta antibody and negative anti-HBs for at least six months, with ALT/aspartate aminotransferase (AST) levels higher than 1.5 times the upper limit of normal, and moderate-to-severe active hepatitis shown by liver biopsy.

Exclusion Criteria

Patients with an accompanying infection with hepatitis C virus (HCV), non-hepatotropic viruses such as human immunodeficiency virus, herpes simplex virus, cytomegalovirus and Epstein-Barr virus, patients with heavy alcohol consumption (more than 8 drinks per week), those using drugs (that may induce hepatitis) and herbal medicines, and patients having autoimmune hepatitis, hepatic ischemia and pregnancy-related liver disease were excluded from the study.

Biochemical and Hematological Markers

Biochemical [albumin, globulin, lactic dehydrogenase, total bilirubin, ALT, AST, creatinine, glucose, alkalen phosphatase (ALP), gama glutamyltranspeptidase and alpha-fetoprotein (AFP)] and hematological (ferritin, serum iron, serum iron binding capacity, leukocyte, hemoglobin, platelet, and prothrombin time) parameters were analyzed in all patients. Biochemical parameters were analyzed using an Architect C16000 device and complete blood count was analyzed using an Abbott CELL-DYN 3700 device.

Serological and Virological Testing

The serological markers of HBsAg, anti-HBs, hepatitis B e (HBe) antigen and anti-HBe were tested by macro-ELISA method, whereas anti-delta immunoglobulin (Ig) M and anti-delta IgG were tested by micro-ELISA method. HDV RNA level was analyzed by real time reverse transcriptase polymerase chain reaction (PCR) (ABI-PRISM/7700 Sequence Detector, AJ RoboscreenGmBH, Germany) method, whereas HBV DNA was analyzed by COBAS Ampli Prep/CobasTaq Man HBV test (ROCHE, USA).

Liver Biopsy

Liver biopsy was planned for histological examination in patients with CHB and CHD. Fine needle biopsy was performed using the Menghini technique under the guidance of ultrasonography. All biopsies were stained with hematoxylin-eosin for grading necroinflammation and reticulin for the assessment of fibrosis. Biopsy materials were blindly evaluated by a single pathologist. Histologic scoring was done using the Ishak-modified histology activity index (10). Fibrosis was assessed according to Ishak fibrosis score. The Ishak system has more stages of fibrosis (0-6) when compared to other systems (11). Because of having the ability to differentiate milder changes in fibrosis more clearly, the Ishak staging system has been widely used in clinical trials (12).

Statistical Analysis

Statistical analysis was done by 'SPSS 16.0 for Windows' package program. The results were presented as mean ± standard deviation. Pearson's or Spearman's correlation coefficient was used to analyze correlations. A p value of less than 0.05 was considered statistically significant.

Results

Clinical and Demographic Data (Table 1)

A total of 220 patients with a mean age of 38.04 years, of whom 75 (34.09%) were female and 145 (65.90%) were male, participated in the study. In patients with DA cirrhosis; 16 (36.36%) of 44 patients were female and 28 (63.64%) were male with a mean age of 44.37±12.42 years. In patients with CHD; 31 (36.04%) of 86 patients were female and 55 (63.96%) were male with a mean age of 37.92 years. In patients with CHB; 28 (31.1%) of 90 patients were female and 62 (68.9%) were male with a mean age of 35.06 years. Demographic, biochemical and serological characteristics of these groups are shown in Table 1.

The mean age of the patients in DA cirrhosis was significantly higher than in CHD (p=0.006) and CHB (p<0.001).

Biochemical and Hematological Data

Analysis of biochemical and hematological data are shown in Table 1. ALP levels in DA cirrhosis were significantly higher than in CHB (p<0.001). ALP levels in CHD were significantly higher than in CHB (p=0.001). Serum albumin levels in DA cirrhosis patients were significantly lower than in CHD and CHB patients. Globulin levels in DA cirrhosis were significantly higher than in CHD (p<0.001). Globulin levels in DA cirrhosis was also significantly higher than in CHB (p<0.001). Ferritin levels in DA cirrhosis were found to be significantly higher than in CHD (p=0.032) and CHB (p=0.010); whereas, no significant difference was found when CHD was compared with CHB (p=0.848). AFP levels in DA cirrhosis were significantly higher than in CHD (p=0.029) and CHB (p<0.001); whereas, no significant difference was found between CHD and CHB (p=0.270). Distribution of demographic, biochemical, hematological and virological characteristics of study participants among groups are shown in Table 1.

Serological Data

HBV DNA levels in DA cirrhosis group were significantly lower than in CHB group (p<0.001). HDV RNA levels were found to be 4.35±1.41 (Log_{10}) copies/mL in patients with DA cirrhosis and 4.69±1.63 (Log_{10}) copies/mL in patients with CHD. No significant

Table 1. Univariate analysis of demographic, biochemical and hematological parameters of all patient groups

Variable	Group 1: HDV related liver cirrhosis (n=44)	Group 2: Chronic delta hepatitis (n=86)	Group 3: Chronic hepatitis B (n=90)	p (1-2)	p (1-3)	p (2-3)
Age	44.37±12.42	37.92±12.07	35.06±9.53	0.006	<0.001	0.208
Gender (F/M)	16/28	31/55	28/62	-	-	-
ALT (U/L)	83.64±62.98	94.83±100.37	80.57±60.56	0.725	0.976	0.456
AST (U/L)	96.14±73.90	70.21±112.61	50.50±45.29	0.213	0.009	0.259
ALP (U/L)	118.00±54.46	103.12±47.10	79.51±25.98	0.134	<0.001	0.001
GGT (U/L)	96.14±109.50	62.76±56.79	59.73±122.13	0.167	0.115	0.978
Albumin (g/dL)	3.26±0.53	4.02±0.43	4.12±0.35	<0.001	<0.001	0.321
Globulin (g/dL)	4.53±0.92	3.87±0.78	3.43±0.48	<0.001	<0.001	<0.001
T.Bilirubin (mg/dL)	1.72±1.34	1.00±1.55	0.82±0.55	<0.001	<0.001	<0.001
Creatinine (mg/dL)	0.80±0.20	0.85±0.19	0.89±0.19	0.353	0.025	0.289
Glucose (mg/dL)	112.11±46.65	102.22±38.85	94.83±23.19	0.286	0.022	0.348
LDH (U/L)	251.36±118.92	209.43±97.98	206.94±92.57	0.065	0.045	0.985
Hemoglobin (g/dL)	12.54±2.04	14.32±1.68	14.74±1.66	<0.001	<0.001	0.260
Leukocyte (mm^3)	4559.09±2172.68	6221.77±2108.35	6787.67±1492.03	<0.001	<0.001	0.119
Platelet (mm^3)	87281.82±40736.11	173096.51±56620.97	226788.89±55345.39	<0.001	<0.001	<0.001
INR	1.39±0.23	1.23±0.96	1.04±0.14	0.339	0.007	0.113
Iron (u/dL)	90.33±53.97	101.34±46.24	103.93±46.65	0.440	0.290	0.935
SIBC (u/dL)	227.49±116.96	252.45±85.46	228.39±79.02	0.305	0.998	0.201
Ferritin (u/dL)	293.25±483.88	156.33±186.00	131.85±232.99	0.032	0.010	0.848
AFP	8.44±9.48	4.97±8.17	3.23±4.12	0.029	<0.001	0.270
HBV DNA Log_{10} (IU/mL)	3.42±1.05	3.84±1.09	5.31±1.70	0.466	<0.001	<0.001
HDV RNA Log_{10} (copies/mL)	4.35±1.41	4.69±1.63	-	0.335	-	-
Necroinflammation score, grade	-	9.30±2.89	5.95±2.82	-	-	<0.001
Fibrosis stage	-	3.14±1.24	1.94±1.40	-	-	<0.001

Note: P (1-2): p value of comparison for group 1 and 2; P (1-3): p value of comparison for group 1 and 3; P (2-3): p value of comparison for group 2 and 3.
F: Female, M: Male, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkalen phosphatase, GGT: Gama glutamyltranspeptidase, T.Bilirubin: Total bilirubin, LDH: Lactic dehydrogenase, INR: International normalized ratio, SIBC: Serum iron binding capacity, AFP: Alpha-fetoprotein, HBV: Hepatitis B virus, HDV: Hepatitis delta virus

difference was found between these two groups in terms of HDV RNA levels (p=0.335). Virological characteristics of study participants are shown in Table 1.

Histological Data

Based on the liver biopsy findings of the study participants, the mean histological activity score (necroinflammation), which was calculated according to Ishak's scoring system, was 9.30±2.89 in CHD and 5.95±2.82 in CHB. It was significantly higher in CHD than in CHB (p<0.001). Comparing the fibrosis stage between CHD and CHB, CHD patients had higher fibrosis stage than CHB patients (p<0.001). Histopathological findings of the study participants are shown in Table 1.

Correlation Analysis

A significant correlation was found between fibrosis stage and HDV RNA levels (r=0.572, p=0.002) (Figure 1). No significant correlation was found between HDV RNA and ALT and AST levels (p=0.743 and p=0.347, respectively).

A significant correlation was found between necroinflammation score and ALT in CHD (r=0.350, p=0.021). The results of correlation analysis in CHD group are shown in Table 2.

HBV DNA levels were significantly correlated with both ALT (r=0417, p<0.001) (Figure 2) and AST levels (r=0.344, p=0.001) (Figure 3) in CHB group. HBV DNA levels were not correlated with necroinflammation scores (r=0.139, p=0.237) and fibrosis stage (r=0.141, p=0.231) in CHB. ALT levels were significantly correlated with necroinflammation score (r=0.290, p=0.010); however, no significant correlation was found between ALT levels and fibrosis stage (r=0.191, p=0.096). While AST levels were correlated with necroinflammation score (r=0.385, p=0.001); it was not correlated with fibrosis stage (r=0.193, p=0.092). The results of correlation analysis in CHB are shown in Table 3.

Discussion

HDV is a defective RNA virus and causes infection using HBsAg. There have been a limited number of studies investigating factors playing a role in clinical manifestations and events observed during natural history of the disease in patients with CHD and the dominant virus in the progression of disease. In the present study, we aimed to investigate clinical, virological and histological characteristics of patients with CHD and with HDV-positive cirrhosis and to compare with those in patients with CHB.

In their study including 48 HBsAg- and anti HDV-positive patients, Yamashiro et al. (13) reported that the mean age of cirrhotic patients (65.9±9.3 years) was higher than that of asymptomatic patients (61.8±16.4 years) and patients with CHD (54.2±12.0 years) (p<0.05 and p<0.05, respectively). Wu et al. (14) reported in their study including 185 patients that the mean age was 43±16 years in patients with CHD and 54±10 years in cirrhotic patients. In our study the mean age of patients in DA cirrhosis, CHD and CHB was 44.37±12.42 years, 37.92±12.07 years and

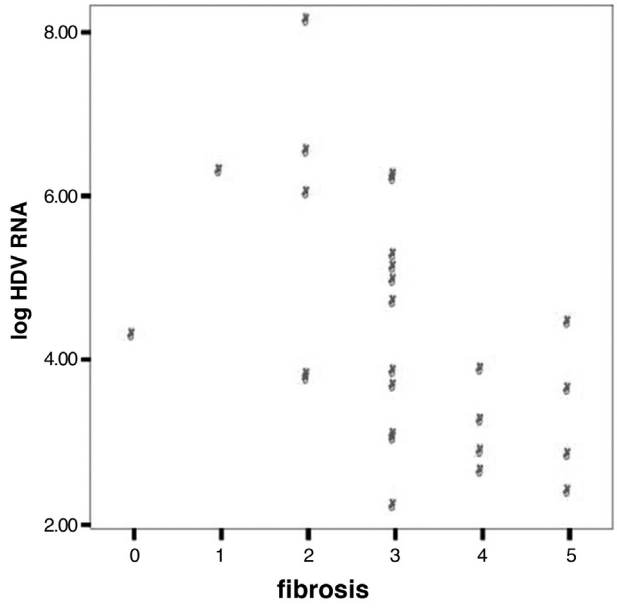

Figure 1. Relation between Log hepatitis delta virus RNA and fibrosis stage in chronic delta hepatitis group (r=0.572, p=0.002)
HDV: Hepatitis delta virus

Table 2. Results of correlation analysis in the patients with chronic hepatitis D

		Log HDV RNA	Log HBV DNA
Spearman's rho NIA	Corr. coefficient p n	0.350 p=0.08 26	0.079 p=0.691 28
Stage	Corr. coefficient p n	0.572 (**) p=0.002 26	0.046 p=0.815 28
ALT	Corr. coefficient p n	0.049 p=0.743 47	0.198 p=0.168 50
AST	Corr. coefficient p n	0.140 p=0.347 47	0.222 p=0.121 50

**Correlation is significant at the level of 0.01 (2-tailed), *Correlation is significant at the level of 0.05 (2-tailed)
HBV: Hepatitis B virus, HDV: Hepatitis delta virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, N/A: Not applicable

Table 3. Results of correlation analysis in the patients with chronic hepatitis B

		Log HBV DNA
ALT	Pearson correlation p n	0.417 (**), p<0.001 87
AST	Pearson correlation p n	0.344 (**), p<0.01 87
NIA	Pearson correlation p n	0.139 p=0.237 74
Stage	Pearson correlation p n	0.141 p=0.231 74

**Correlation is significant at the level of 0.01 (2-tailed), *Correlation is significant at the level of 0.05 (2-tailed)
HBV: Hepatitis B virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, N/A: Not applicable

35.06±9.53 years, respectively. Cirrhotic patients were older than non-cirrhotic subjects (p<0.01), consistent with previous studies. On the other hand, we have found that the mean age of patients with DA cirrhosis was lower than reported in previous studies. This difference arises from the presence of higher number of new cases among study participants and indicates perinatal transmission of both viruses HBV and HDV. Therefore, it indicates the importance of vaccination against HBV in eradication of delta hepatitis.

Yamashiro et al. (13) reported that there was no statistically significant difference in mean ALT levels between patients with CHD and those with cirrhosis (130.7±214.1 and 84.4±65.3, respectively) but asymptomatic patients had significantly lower ALT levels as compared to CHD group (p<0.05) and cirrhosis group (p<0.05). Wu et al. (14) reported higher ALT levels than in our study. In our study, AST level was found to be significantly higher in DA cirrhotic patients as compared to the group with CHB (p=0.009). We also found that the albumin level was significantly lower in DA cirrhosis as compared to non-cirrhotic patients (p<0.001). No significant difference was found between patients with CHD and CHB (p=0.321). This result supports the previous study of Yamashiro et al. (13) because in that study, albumin level was not found to be statistically significantly different between cirrhosis (4.4±0.8), CHD (4.5±0.5) and asymptomatic (4.5±0.5) patient groups. In the present study, platelet count was found to be significantly lower in cirrhotic patients as compared to that in patients with CHD and patients with CHB infection (p<0.001, p<0.001). Platelet count was significantly lower in the CHD as compared to the CHB patients (p<0.001). These results appear to support the results of a similar study existing in the literature (13).

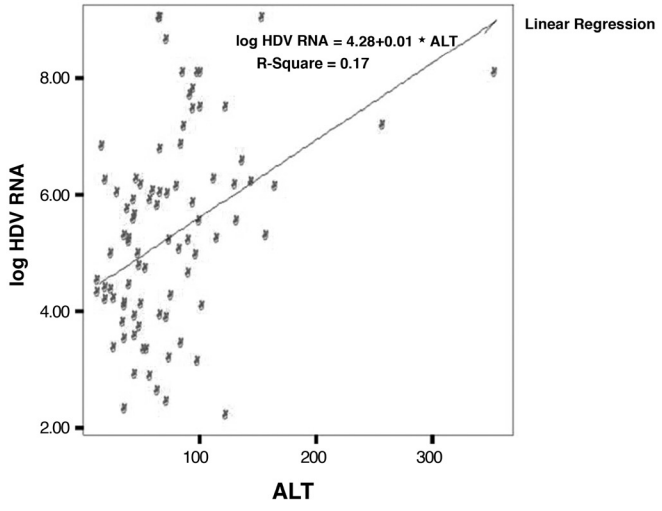

Figure 2. Relation between Log hepatitis B virus DNA and alanine aminotransferase in chronic hepatitis B group
ALT: Alanine aminotransferase, HDV: Hepatitis delta virus

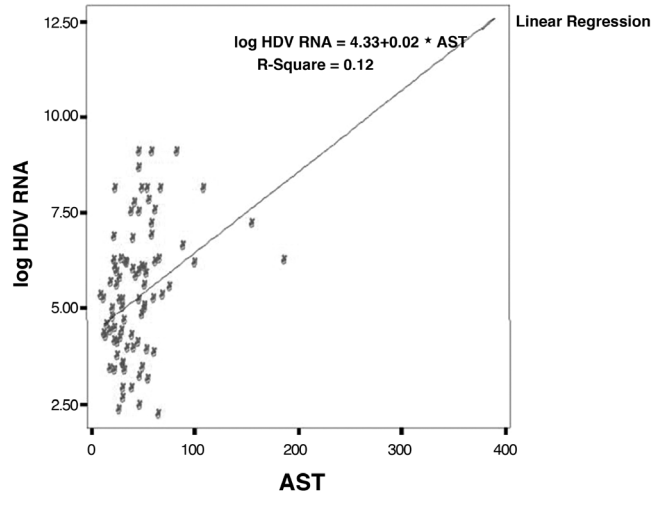

Figure 3. Relation between log hepatitis B virus DNA and aspartate aminotransferase in chronic hepatitis B group
AST: Aspartate aminotransferase, HDV: Hepatitis delta virus

In the present study, there was no statistically significant difference in HBV DNA level between patients of DA cirrhosis (3.42±1.05 Log_{10} copies/mL) and CHD (3.84±1.09 Log_{10} copies/mL) (p=0.466). However, HBV DNA levels in DA cirrhosis patients were significantly lower as compared to patients with CHB (5.31±1.70) (p<0.001). Likewise, HBV DNA levels in patients with CHD were found to be significantly lower as compared to that in patients with CHB infection (p<0.001). HDV RNA level was not significantly different between patients with DA cirrhosis and patients with CHD (p=0.335). Yamashiro et al. (13) found no difference between the patient groups (asymptomatic, chronic hepatitis and cirrhosis) in terms of HBV DNA levels. Wu et al. (14) found that HDV RNA level was the highest in patients with acute hepatitis (98%), whereas it was found at decreasing concentrations (74%, 74%, 63%) in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma, respectively (p=0.002). HBV DNA level was the lowest in patients with acute hepatitis (61%) as compared to the other groups (66%, 70%, 80%) (p=0.002), and consequently, they concluded that HDV was more dominant in the progression of disease (14). The results of our study revealed that HBV DNA levels were not statistically different between DA cirrhosis patients and patients with CHD. This result is similar to the result of the study conducted by Yamashiro et al. (13). However, HBV DNA levels in both groups were significantly lower than that in patients with chronic HBV infection. This outcome indicates not only suppressive character of HDV on HBV, but also supports the hypothesis that delta hepatitis is the primary agent responsible for progression of the disease (14).

In the present study, a correlation was found between serum HDV RNA and fibrosis stage. The findings indicated that HDV RNA positively correlated with necroinflammatory activity as well. It was also revealed that HDV RNA positively correlated with ALT level in CHD patients. In a study conducted by Braga et al. (15), mean HDV-RNA showed positive correlation with inflammatory activity and fibrosis stage. HDV viral load was correlated positively with serum levels of liver enzymes and inversely with platelet count. HBV viral load showed no correlation with any of the above-mentioned parameters. As a consequence, HDV may possibly play an important and direct role in the development of necroinflammatory activity and fibrosis. The results of our study confirm the findings in the study conducted by Braga et al. (15).

Higher necroinflammation score and advanced stage of fibrosis and accordingly more severe disease were observed in patients with CHD (9.30±2.89) than in patients with CHB (5.95±2.82) (p=0.001). In a study from Turkey conducted by Albayrak et al. (16),

12 patients with CHD underwent biopsy and the mean fibrosis stage was found to be 1.91±1.22 and mean necroinflammation score was found to be 8.92±1.83. While necroinflammation score was similar with that in our study, fibrosis stage was lower than in our study.

Conclusion

Our study revealed that age of onset of hepatitis and, accordingly, age of onset of related liver cirrhosis are lower in Turkey. ALT levels are not different between patients with CHD, DA cirrhosis and CHB. HBV DNA appears to be suppressed in patients with delta hepatitis as compared to patients with CHB. Histologically more severe findings were observed in patients with CHD and in HDV-positive cirrhotic patients. These results support the hypothesis that delta hepatitis together with hepatitis B plays a role as the dominant factor and accelerates disease progression.

Ethics

Ethics Committee Approval: Retrospective study.
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.Y., Concept: M.S.Y., K.Y., Design: M.S.Y., K.Y., Data Collection or Processing: M.S.Y., Analysis or Interpretation: M.S.Y., K.Y., Literature Search: M.S.Y., K.Y., Writing: M.S.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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