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Seroprevalence of Delta Hepatitis in Chronic Hepatitis B Patients: Single Center Study

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Objective: Hepatitis B virus (HBV) infection is an important health problem in Turkey. Mortality and morbidity rates arise by accompanion of Hepatitis D infection (HDV). Prevalence of Hepatitis Delta virus (HDV) in HBV-positive individuals varies according to the regions in Turkey with 20% occurence in the western and up to 46% in the eastern parts. The aim of this study is to assess the presence of HDV in HBV patients applying to the center of our study.

Materials and Methods: A total of 1025 patient records were reviewed retrospectively. Eighty-four were excluded due to insufficient case data; the remaining 941 patients were included in the review process. Patients were divided into those with chronic hepatitis B (group A) and those with liver cirrhosis (group B). HDV presence in both groups was assessed and compared between each group.

Results: Of all 941 patients included in the study, 857 (91%) had chronic hepatitis B (Group A) and 84 (9%) had liver cirrhosis (Group B). Among group A patients, 62% were male and 38% were women; average age was 42±13 years. Group B patients were 77% male and 23% female; mean age was 54±14 years. Among all patients, HDV seropositivity was 3.4%, with 1.8% among group A patients and 20% in Group B (P= 0.001). Results were assessed by Chi-Square test and t–test. Group B patients were found to have significantly higher age (P= 0.007) and HDV seropositivity (P= 0.004) compared to group A patients.

Conclusion: Cirrhotic patients were found to have 11-fold higher presence of HDV compared to non-cirrhotic patients.

***Key words**: Hepatitis B, Hepatitis D, seroprevalance, cirrhosis*

Kronik Hepatit B Hastalarında Delta Hepatit Seroprevalansı: Tek Merkez Çalısması

Amaç: Hepatit B virüs (HBV) infeksiyonu Türkiye'de önemli bir sağlık problemidir ve Hepatitis D infeksiyonu (HDV) ile birlikte olması ile mortalite ve morbidite artmaktadır. HDV prevelansı Türkiye'nin batı bölgesinde %20 iken Doğu Anadolu Bölgesinde %46 olarak farklılıklar göstermektedir. Bu çalışmanın amacı hastanemize gelen HBV hastalarındaki HDV seroprevalansı saptamaktır.

Gereç ve Yöntem: Toplam 1025 hastanın kayıtları retrospektif olarak incelendi. 84 kişinin verileri yetersiz olduğundan dışlandı. Kalan 941 hastaya ait kayıtlar değerlendirildi. Hastalar Kronik Hepatit B (Group A) ve Siroz (Group B) olarak ayrıldı. Her iki grup arasında HDV infeksiyonunun bulunması açısından karşılaştırma yapıldı.

Bulgular: 941 hastanın 857'si (%91) kronik Hepatit B (Grup A), 84'ü (%9) sirotik (Grup B) idi. Grup A daki hastların %62'si erkek, %38'i kadın olup yaş ortalaması 42±13 yıldı. Grup B deki hastaların %77'si erkek ve %23'ü bayan olup yaş ortalaması 54±14 yıldı. Grup B de yaş ortalaması daha yüksekdi (P= 0.015) Total hastalarda HDV seropozitifliği %3.4 olup, Grup A da %1.8, Grup B de %20 idi, Grup B de HDV pozitifliği yüksekti (P= 0.001). Sonuçlar ki kare ve t test ile değerlendirildi. Her iki grupta da erkek cinsiyet olması kadın cinsiyet olmasına göre daha yüksek oranda görüldü (Grup A da P= 0.007, Group B de P= 0.004) Sonuçlar istatistiksel olarak alamlı bulundu.

Sonuç: Çalışmaya katılan tüm hastlarda %3.4 oranında HDV seropozitifliğ saptanmıştır. Sirotik hastlarda ise (%20), kronik hepatit B (%1.8) hastalarından 11 kattır.

***Anahtar Kelimeler:** Hepatit B, Hepatit D, seroprevalans, siroz*

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Introduction

Hepatitis D virus (HDV) was first detected in patients with a more severe form of hepatitis B virus (HBV) infection in 1977 (1). It was identified in both liver biopsies andserum of such patients by means of a novel antigen, designated as the δAg (Delta antigen) (2). Later, HDV was found to be an infectious agent separable from HBV. For both viruses, the only susceptible cells are liver hepatocytes. HDV, similarly to HBV, is a blood-borne infection, and may be transmitted by parenteral routes. For example, both are readily transmitted by contaminated needles shared in intravenous drug use. Unlike HBV, HDV is not typically a sexually transmitted disease, although such transmission may sometimes occur (3).

HDV affects an estimated 15 to 20 million individuals worldwide, and the clinical significance of HDV infection is more severe forms of viral hepatitis (acute or chronic), and a higher risk of developing cirrhosis and hepatocellular carcinoma in comparison to HBV monoinfection (4). HDV infection is diagnosed by high titres of Immunoglobulin G (IgG) and Immunoglobulin M (IgM) anti-HDV, and confirmed by detection of HDV RNA

in serum. The first step in the diagnosis of HDV is screening for antibodies against HDAg (anti-HDV IgM and IgG) in HbsAg-positive individuals. In patients with the anti-HDV reagent, the next step is to screen for HDV RNA in the serum to determine whether the presence of the antibody against HDAg reflects a persistent active infection (HDV RNA positive) or only represents a decreasing serological scar (HDV RNA negative). Although significant advances have been made in the treatment of chronic viral hepatitis over the past decade, targeting HDV remains a major challenge because of the unconventional nature of this virus and the severity of its disease (5). Treatment of HDV is the use of pegylated interferon alfa; however, response rates are poor. Increased understanding of the molecular virology of HDV will identify novel therapeutic targets for this most severe form of chronic viral hepatitis. Moreover, HDV infection is difficult to treat. HBV and HDV are transmitted parenterally via infected blood or body fluids (6-9).

IFN-α still remains the only drug currently used for the treatment of HDV infection. IFN-α induced only a 10% to 20% rate of sustained HDV clearance and a 10% rate of HBsAg clearance. The efficacy of standard IFN-α in combination with ribavirin or lamivudine was not significantly higher than that of IFN-α monotherapy in chronic hepatitis D (7, 8). Similar results were obtained when pegylated IFN-α was used in combination with ribavirin or adefovir. In the largest randomized trial, HIDIT (Hep-Net International Delta Hepatitis Intervention Trial-1), pegylated IFN-α either alone or in combination with adefovir was compared to adefovir monotherapy (9).

HDV epidemiology in different regions of the world is varies. As HDV is dependent on HBV for its replication, it can only infect those people who are simultaneously infected with HBV (coinfection) or who are already carriers of HBV (super infection). Hadler and Fields defined four broad classifications of HDV infection: (1) very low endemicity when HDV prevalence is 0 to 2% in asymptomatic HBV carriers and less than 10% in patients with chronic hepatitis B; (2) low endemicity when HDV prevalence is 3 to 9% in asymptomatic HBV carriers and 10 to 25% in patients with chronic hepatitis B or cirrhosis; (3) moderate endemicity when prevalence is 10 to 19% in asymptomatic HBV carriers and 30 to 60% in patients with chronic hepatitis B; and (4) high endemicity when prevalence is above 20% in asymptomatic carriers and above 60% in patients with chronic hepatitis B (10-14).

HDV prevalence varies widely. Hepatitis D virus (HDV) infection is present worldwide and affects all age groups. Its prevalence is higher in some parts of Africa, South America, Romania, Russia and the Mediterranean region included Southern Italy (15). It is also noteworthy that approximately 5% of the global HBV carriers are co-infected with HDV. Out of approximately 350 million carriers of HBV worldwide, 18 million people are infected with HDV (16). Hepatitis delta virus (HDV), a satellite virus of HBV is endemic in several regions of the World (17, 18).

In some countries, such as Italy, HDV endemicity is variable. HDV appears to be endemic in the general population of southern Italy. By contrast, HDV infection in northern Italy predominates among southern emigrants in industrial towns and parenteral drug users (19). In the United States, the prevalence of HDV infection in the general population is low. The prevalence of HDV infection in HBsAg-positive volunteer blood donors varies from as low as 1.4% in one southeastern region of the country to 12.4% in Southern California (20, 21).

In Turkey, A recently published meta-analysis of HDV seroprevalence indicated a decline in HDV infections (22, 23). The HDV prevalence in chronic hepatitis B patients was found to be 27% in the Southeast Turkey and 12% in the Central Turkey. HDV prevalence in cirrhosis patients has been reported as 46% in the Southeast and 20% in the Western Turkey (23).

In association with HBV, HDV produces significantly more severe illness than HBV alone. HDV is now well known to induce a spectrum of both acute and chronic liver diseases. In the present study, a group of HBV-infected patients was involved in order to assess the prevalence of HDV infection in the last decade in Turkey. In addition, we assessed effects of HDV/HBV coinfections on the clinical staging of HBV-related liver diseases.

Materials and Methods

A retrospective review of HBsAg-positive specimens was carried out on the records of the patients with chronic hepatitis B or hepatitis B induced-cirrhosis who have been on follow-up in our hospital, during the last 10 years.

A total of 941 HBsAg-positive patients were included in the study. The retrospective data collection of HbsAg-positive patients included demographic characteristics, liver function tests, abdominal US reports,viral hepatitis markers including HBsAg, HbeAg, Anti-HBe, Anti-HDV total (IgM + IgG), HBV DNA and HDV RNA values and liver biopsy results. For the study, all biochemical, hematological and virological tests were performed at laboratories of our centers. Serum samples were tested for serological markers for hepatitis (HBsAg, antiHBs, antiHBc, HBeag, AntiHBe) using microparticle enzyme immunoassay (MEIA) technique (The COBAS® TaqMan® 48 analyzers) samples that were found positive for HBV were included in this study. HDV Ab test was ordered for all patients. For HDV Ab positive patients, qualitative HDV RNA PCR was performed in order to identify viremic cases. Furthermore, in order to assess advanced liver disease (cirrhosis), clinical evaluations and if needed, complementary tests, liver sonography, fibroscan, and liver biopsy were performed. Additionally, standard questionnaires containing demographic and high-risk behaviors characteristics were completed for each patient.

Total anti-HDV levels in the HbsAg-positive samples were then determined using enzyme-linked immunosorbent assay method. Out of these, anti-HDV ELISA positive samples were further analyzed by HDV RNA PCR. HBV DNA were analyzed by PCR samples that were found positive for HBsAg. The serum HBV DNA and HDV RNA amount was determined by quantitative PCR assay with a detection limit of 100 copies/ml in patients with chronic hepatitis B + D.

Biopsy specimens were stained with hematoxylin and eosin, and the histological activity index (HAI) of chronic hepatitis patients was determined according to Knodell's scoring system.

Chronic hepatitis B infection was defined in patients who had HBsAg present for more than 6 months with serum HBV-DNA>20.000 IU/mL in HBeAg-positive patients, and with HBV DNA>2000 IU/ml in HBeAg negative patients, with normal or elevated AST and/or ALT level, and if liver biopsy or noninvasive test results show chronic hepatitis with moderate or severe necroinflammation and with or without fibrosis. Group A included Chronic Hepatitis B patients, Group B included cirrhotic patients.

The statistical evaluation of the data was undertaken using the SPSS 15.0 program. The Chi-Square test and independent-samples t-test were used to assess the significance of the difference among the ratios in the advanced analysis. P-value <0.05 was considered to be significant.

Results

In this study, we investigated the prevalence of HDV among the patients who have been on follow up in our hospital during the last 10 years due to chronic hepatitis B or hepatitis B-induced cirrhosis. Clinical and laboratory data of patients with chronic hepatitis B infection and those with liver cirrhosis were included in the study.

Demographic characteristics of the patients are shown in Table 1. A total of 941 patients were included in the study. The majority of patients (n= 857; 90 %) were Chronic hepatitis B (Group A) (n= 857, 90%) (P=0.003) (Table 1). 857 (91%) had chronic hepatitis B in Group A and 84 (9%) were cirrhotic patients in Group B. The number of patients in chronic hepatitis B group was higher than cirrhosis group. This result was statistically significant (P= 0.003).

596 patients were male (63%) and 345 patients were female (37%) and the mean age of the patients in the Group A was 42±13 years and the mean age was 54±14 years in the Group B. There was a statistically significant difference between the Group A and Group B in terms of age P= 0.015. The mean age of the Group B higher then the mean age of the Group A (Table1).

By comparison of male patients with female patients the number of male patients were higher than female patients in Group B (n= 65, 77% versus n= 19, 33% respectively) (P= 0.004). There was a statistically significant difference. Similarly, the number of male patients was higher than female patients (n= 531, %62, n= 326, 38% respectively) in Group A, and this result was statistically significant (P= 0.007).

Out of 941 patients with hepatitis B, 32 were HDV positive. The data on the prevalence of HDV among the patients with chronic hepatitis B and cirrhosis are shown in Table 2. Thirty two patients (3.4%) were found to be seropositive for HDV, but when analyzed by the subgroups, 15 patients (1.8%) patients in the Group A and 17 patients (20%) in the Group B were found to be seropositive for HDV. There was a statistically significant difference between the Group A and Group B in terms of anti-HDV-IgG seropositivity (P= 0.001). (Table 2) Similarly, The number of total patients in Group A (n= 857, 91%) was higher than in Group B (n= 84, 9%), which was statistically significant

Table1. Clinical char acteristics of 941 patients witch chronic hepatitis B

Clinical Groups	Male		Female		Age (years)	P Value
	n/total	(%)	n/total	(%)		
Chronic hepatitis B CHB (Group A)	531/857	62	326/857	38	42±13	<0.05
Chronic patients LC (Group B)	65/84	77	19/84	23	54±14	

Values given are medians and ranges or percentile where appropriate Kruskal-Wallis test. Chi-square test.
CHB, chronic hepatitis B; LC, liver cirrhosis

Table 2. Distributions of HDV seropositivity in patients witch chronic hepatitis B and liver cirrhosis

Clinical Groups	HDV/HBV Coinfection		HBV Monoinfection		P Value
	n/total	(%)	n/total	(%)	
Chronic hepatitis B (Group A)	15/857	1.8	862/857	91.2	<0.05
Chronic patients (Group B)	17/84	20	15/84	80	

Chi-squared test was used to analyze the data obtained fro m the study. P value less than 0.05 was accepted as statistically significant sp: seropositivity.

Discussion

Delta hepatitis is still a major global health problem affecting 15-20 million individuals worldwide. HDV coinfection or super infection means that the host liver cells have previously been infected with hepatitis B virus. HDV coinfection or super infection leads to the cirrhosis of the liver and finally hepatocellular carcinoma (HCC) or liver cancer (24-27). Recent studies have indicated that the prevalence of Delta hepatitis displays regional variations in Turkey Türkdoğan et al. (28) investigated the prevalence of chronic delta hepatitis in Eastern Anatolia (n=75) and they found that the rate of delta hepatitis among the cases of chronic hepatitis was 16.2% and 45.3% among the cases of cirrhosis.

Later on the data obtained from 6734 patients were analyzed in a meta-analysis conducted by Değertekin et al. (29) out of these 6734 patients, 5231 were diagnosed with chronic hepatitis and 1503 were diagnosed with cirrhosis and the data obtained from these patients were divided by region into three groups: the Southeast Turkey, Central Turkey and Western Turkey. The prevalence of hepatitis D in each region was calculated separately for either patients with chronic hepatitis or patients with cirrhosis. Based on the results, the rate of Delta hepatitis in the Southeast Turkey was found to be 46% in cirrhotic patients (LC) and 27.1% in patients with chronic hepatitis B (CHB). The rate of delta hepatitis in LC patients and CHB patients were found to be 20% and 12.1% in the Central Turkey Group respectively, and 20% in LC patients of the Western Turkey Group.

The prevalence of HDV infection in Turkey displays variations by region as well as by year The studies conducted by Değertekin et al. (23) indicated that the prevalence of HDV was higher in the East of the country in comparison to the Western regions and has been gradually declining over the years.

In addition, in a study conducted by Kose et al. (30) in the western regions revealed that the rate of HDV IgG positive patients was 2.5% in 3094 HBsAg positive patients (53% inactive hepatitis B carriers).

Furthermore, Dulger et al. (31) conducted a study to identify the socio-epidemiological risk factors associated with HBV infection. They showed that the majority of patients (n = 1480; 55.8%) were residents in the rural areas. They detected Anti-HDV-IgG in 18.4% of tested subjects who came from an urban area, 12.5% of subjects of the rural group had a positive result for anti-HDV-IgG. Delta hepatitis patients, 37.3% had liver cirrhosis, 7% in patients with hepatitis B monoinfection had liver cirrhosis.

Sanou et al. (32) monitored the seroprevalence of HBV-HDV co-infection in different population groups in the Western part of Burkina Faso, and described the genetic diversity of the detected virus strains.

In Turkey, HBV infection rates range from 2.5% to 20% in the general population, 20% to 40% in the cirrhotic patients (22, 23, 29-31), suggesting a high prevalence of HDV infection in HBsAg positive patients. Few studies only have assessed the epidemiological and clinical importance of HDV infection in Turkey, indicating different results in terms of HDV infection prevalences across regions. HDV infections are rather rare in Europe due to largely effective HBV vaccination programs and screening of blood products, hepatitis D remains of concern with highest rates in low-income HBV-endemic countries with insufficient HBV vaccination coverage (33). Due to deficiencies and low socio-economic conditions in vaccination programs for HBV in eastern parts of our country the prevelence of HBV and HDV infection is higher than the western region.

In our study, 1.8% of the patients with chronic hepatitis B and 20% of the cirrhotic patients were HDV seropositive. The seroprevalence for HDV in overall patients with hepatitis B was 3.4%. In our study, the prevalence of HDV was found to be lower than that of the Eastern regions since our hospital is located in the Western part of the country. These results are in line with the previous studies. Interestingly, higher rates of anti-HDV IgG seropositivity were observed in patients with cirrhosis (23).

As shown in the previous studies, our study indicated the rate of patients HDV positive patients was higher in hepatitis B patients with cirrhosis, in comparison to the hepatitis B patients without cirrhosis. The rate of HDV positive patients in the Group A was found to 11-fold higher in comparison to the Group B. Our results are important because of that they support the previous studies and include patients with follow-up in a single center. Our finding demonstrate that HDV infection is not rare in this country. HBV/HDV co-infection can cause more severe liver disease than HBV mono-infection, resulting in accelerated progression of cirrhosis. The higher prevalence of HDV in cirrhotic patients suggests that HDV is associated with poor prognosis. These results are in line with the results of the previous studies performed in our country and suggest that HDV is endemic in Turkey.

The higher prevalence of HDV in cirrhotic patients suggests that HDV is associated with poor prognosis. These results are in line with the results of the previous studies performed in Turkey (34) and suggest that HDV is endemic in Turkey.

In conclusion this study shows that 3.4% of the patients with hepatitis B patients were seropositive for HDV and its' seroprevalence increases by 11-fold in cirrhotic patients which indicate that HDV increases the severity of liver disease and HDV is endemic in Turkey.

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