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Epidemiology and Risk Factors of Hepatitis Delta Infection in Turkey

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This study is aimed to investigate the prevalence and risk factors of HDV co-infection in patients with chronic HBV infection in Turkey, where HBV infection is endemic. The date of this study was obtained from Turk-Hep-Net project. The project includes real-life cohort of HBV patients from 15 centers in Turkey and is supported by Viral Hepatitis Society. Of the 7366 HBsAg positive individuals tested for the presence of anti-HDV antibodies, 63,6 were male and 36.4 % were female. Of the 7366 HBsAg positif patients, 206 (2.8%) contained anti-HDV. Southeastern Anatolia Region of the country's anti-HDV positivity rate was found to be 4.5%. The risk factors in anti-HDV positivity patient were; male gender, long-term (>5 year) HBsAg positivity and living in Southeastern Anatolia. Our study revealed that recognizing the risk factors associated with HBV and HDV co-infection will be beneficial to control of these infections.

Key words: HDV, HBsAg, Risk factors, Turkey.

Hepatitis B (HBV) is one of the most common public health problems worldwide. In developing countries, this infectious disease causes 1 million deaths per year[1]. Hepatitis Delta virus (HDV) which is a defective RNA virus first defined in 1997 in Italy. This virus requires the presence of HBsAg for replication. After the replication in the nucleus of the hepatocyte, HDV is transferred to cytoplasm, where it is enveloped by HBsAg and secreted into the circulation. Simultaneous infection with HDV leads to progression of chronic HBV infection to chronic active hepatitis, cirrhosis, and hepatocellular carcinoma. The response of HDV patients to treatment and the required dosages of therapeutic regimens differ from those of chronic hepatitis B alone[1-4].

Five percent of HBV carriers are infected with HDV worldwide[2,3]. The prevalence of HDV positivity is higher in Italy, eastern Europe, and western Asia, reaching 83.3%, 8.3%, and 12.5% in Romania, Italy, and Russia, respectively[1].

In endemic regions for HDV, it is transferred by close personal contact in the absence of clear skin contact, such as close personal relationships among members of a family. In contrast, in areas that have a low prevalence,

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such as western Europe and North America, HDV is seen more commonly in groups with frequent skin contact such as continual recipients of blood and blood products and intravenous drug users. Other modes of HDV transmission are sex and maternal-child transmission[1].

Prevalence of HDV decreased in the western countries, recently due to extensive vaccination protocols, control of transfusion medicine and increased socio-cultural level. However HDV infections are still an important public problem in developing countries and also in Turkey. Especially in southeast of Turkey. For this reason we aimed to investigate the prevalence and risk factors of HDV co-infection in patients with chronic HBV infection in Turkey, in this multi-center study.

METHODS

In this study 7366 HBsAg positive individuals tested for the presence of anti-HDV antibodies.The data of this study was obtained from Turk-Hep-Net project. Turk-Hep-Net project includes real-life cohort of HBV patients from 15 centers in Turkey and is supported by Viral Hepatitis Society. The data of HDV-HBV positive patients in Turk-Hep-Net database were complied and analysed, by September 30, 2011. In this study demographic characteristics of the patients were recorded and the Hepatitis B s antigen (HBsAg), Anti-HBs, Hepatitis B e antigen (HBeAg), Anti-HBe, Anti-HBc, anti-HDV and HBV DNA were investigated and recorded. The patients were further investigated for the results of liver function tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gama-glutamyl transpeptidase (GGT), and alkaline phosphatase (AP) levels. Patients with any known other cause of hepatitis, such as hepatitis C, autoimmune hepatitis or primary biliary cirrhosis, were excluded. All the data analysis was carried out using the SPSS software Version 11.0 (SPSS, Chicago, IL, USA). A P-value of <0.05 was considered significant. The study was approved by the local ethics committee.

RESULTS

Of the 7366 HBsAg positive individuals tested for the presence of anti-HDV antibodies, 63,6 were male and 36.4 % were female. The average age +/- standard deviation was 34.4±15.9 years. Of the 7366 HBsAg positive patients, 206 (2.8%) contained anti-HDV. Southeastern Anatolia Region of the country's anti-HDV positivity rate was found to be 4.5%. Anti-HDV positivity was significantly more common in patients with chronic active hepatitis B infection compared to asymptomatic carriers ($p = 0.025$). The risk factor in anti-HDV positivity patient was; male, gender, long-term (>5 year) HBsAg positivity and living in Southeastern Anatolia (Table 1).

DISCUSSION

Hepatitis B virus infecton is one of the most common public health problems worldwide. According to literature, 1.2%-9.7% of the world's population have HBV infection[1]. Turkey is an indermediate endemic area (2%-8%) for HBV infection[5]. Turkey is divided into seven regions

Table 1. Distribution of anti-HDV (+) patients by age, gender, duration of HBsAg positivity, and the inhabited region.

	Anti-HDV (+)	Anti-HDV (-)	P
Asymptomatic carrier (HBV)	33	2248	p>0.05
Chronic active hepatitis B	173	4812	p=0.025
Duration of HBsAg positivity (>5 years)	194	4871	P=0.002
Age	34.5±15.1	34.4±11.4	p>0.05
Gender (male)	158	4527	P=0.041
HBsAg (+) family member	184	5144	P=0.004
Living in Southeastern Anatolia	130	2755	P=0.031
Total	206	7160	

based on geographical characteristics and the prevalence of HBsAg varies by regions[5-7]. In an Eastern Anatolia study, HBsAg prevalence was found to be 9.8%[6]. In a study estimated overall population prevalence of HBV was 4.57, and total number of CHB cases was 3.3 million[5]. As known, HDV requires the presence of HBsAg for replication and HDV hepatitis may lead to 3-fold increase in development of hepatocellular carcinoma and 2-fold increase in mortality compared with HBV infection without HDV[2,3,8]. There was no large-scale study in Turkey evaluating the risk factors for HDV infection. Our study of patients will contribute to the Turkey and world literature.

The prevalance of HDV is higher in eastern Europe and western Asia[1]. The prevalence of HDV among HBsAg-positive individuals has been reported to be 1.5-5.8 in Iran[9-11], 1.5% in Yugoslavia[12], 1.6% in Spain[13], 2.2% in Taiwan[14], 4% in Mexico[15], 24.4% in Bangladesh[16], 12.5% in Russia[17], and 8.3% in Italy[1,18]. In one of the Turkey studies, Bahçecio?lu et al found that 45% of chronic hepatitis B patients were positive for anti-HDV[19]. In another study from Turkey, Çelen *et al*. found that 27.5% of chronic active hepatitis B patients was anti-HDV positive[20]. In our study Of the 7366 HBsAg positive patients, 2.8% was positive for anti-HDV. In light of these results we can say that prevalence of HDV infections has been decreased in Turkey. We thought that the reason for this decline owing to extensive vaccination protocols and control of transfusion medicine in Turkey. However in current study, anti-HDV positivity was 4.5% in the Southeast Anatolia region of Turkey is approximately twice the national average and living in Southeastern Anatolia found to be a risk factor for HDV seroprevalence. The South-eastern Anatolia region is a region with higher population of HBV and most of the people live in rural areas. In this region, the majority of families are crowded and close contact is frequent between family members. That may be why we've found to be a high prevalence. In fact, the studies of Mediterranean countries, including the Middle East were reported that HDV infection is transmitted primarily through noncutaneous routes, especially close personal contact, such as that between family members[1]. In current study and in Turkey studies, family history was found significantly higher among HDV-positive HBV patients when compared to negative ones[19,21]. Mansour et al demonstrated that anti-HDV were more frequent in persons who had been married more than once and they suggested that intra-familial transmission (due to sharing of facilities and overcrowding) may be a source of HDV transmission[22]. Hepatitis D virus transmission and spread of this virus can be prevented by avoidance of an infected individual in close family relationships, and early diagnosis of infection by screening of high-risk persons and their families[1].

On the other hand, it has been reported that phlebotomy, surgery, blood transfusions, and dental manipulations were the other risk factors for HDV positivity[1]. Especially a high prevalence of HBsAg in blood donors has been described in several African countries and Sub-Saharan Africa: 8.65-44% [22-29]. In addition in hyper-endemic areas the major sources of the increasing prevalence have been reported that perinatal transmission and horizontal spread. Therefore in these regions most of the infections ocur during infancy or early childhood[19,21]. In an Iran study, a significant association was observed between HDV positivity and the mother's hepatitis B carrier status and the authors suggested that one of the most important routes of transmission for HBV in Iran may be the horizontal route such as household contact[8].

In many Turkey studies and our study showed that HDV infection is more common in 35-45 years of age group[19-21] but being male was found to be a risk factor for HDV seroprevalence [19-23]. According to literature, military staffs were more likely to be infected by HDV. The authors have been proposed many hypotheses about the high prevalence found in this population. They have been suggested that the vast majority of those people were men and men sexual transmission was common in these subjects, these subjects may have been exposed to health care procedures more often (i.e. vaccination, parenteral antibiotic reatments, etc.), were generally living in communities[22,23]. In Turkey, risk factors such as multi partnership, intravenous drug usage, having shave in barbers, traveling, etc. are more common in male population. Therefore HBV and HDV prevalence is higher in males than females..

Long-term (>5 year) HBsAg positivity was a risk factor in our study. To our knowledge

acute HDV infection can develop simultaneously with acute HBV infection or can be superimposed into chronic HBV infection[1]. In some studies HBsAg levels were also found to be higher in HDV-RNA-positive patients[19,21]. These studies suggested that elevated HBsAg levels rather than HBV DNA levels can provide evidence for HDV replication in patients with chronic HDV[19,21]. Celen. et al found that the prevalence of anti-HDV in asymptomatic hepatitis B carriers was 6% and in chronic active hepatitis B patients with was 27.5%. They showed that the incidence of anti-HDV positivity was significantly higher in patients with chronic active hepatitis B compared with asymptomatic carriers and demonstrated a significant association between the duration of HBsAg carrier status (3.2 +/- 1.4 years) and anti-HDV positivity ($p<0.001$) (20). On the other hand Amini et al found that that HDV was more common among cirrhotic and HCC patients[30]. Romeo et al. observed that 82% and 15% of chronic HDV patients developed cirrhosis and HCC in a study during 233 months of follow-up[31]. Therefore the authors suggested that HDV causes a severe form of chronic hepatitis in comparison with HBV monoinfection and the longer history and more severe condition cause a higher rate of anti-HDV antibody[31]. As a result we can say that elevated HBsAg level leads to increased replication of HDV and long duration of HBsAg positivity increases the likelihood of development super-infection with HDV.

In addition, the course of the disease in HBeAg-positive patients with hepatitis D is not yet clear. Among HDV patients the rate of HBeAg-positivity was reported as 15-30%. Amini et al found that HDV was more common in HBeAg positive persons[31]. However in some studies, any association with HBeAg positivity and anti-HDV positivity was not found[8,20].

In conclusion HDV remains as a major health problem in Turkey. Individuals infected with HBV and HDV are under risk for severe hepatic complications. Our study revealed that the family contact should be prevented by improving of the living conditions in Turkey, the patients with HBV should be screened for HDV and ealy antiviral treatment should be started for this patients. Recognizing the risk factors associated with HBV and HDV co-infection and the reasons behind this regional increase in anti-HDV serology in patient with HBV will be beneficial to control of these infections.

REFERENCES

1. Ataei B, Yazdani MR, Kalantari H, Yaran M, Nokhodian Z, Javadi AA, et al. Hepatitis D virus infection in Isfahan, central Iran: Prevalence and risk factors among chronic HBV infection cases. *Hepat Mon* 2011; **1**(11): 269-272.
2. Ji J, Sundquist K, Sundquist J. A population-based study of hepatitis D virus as potential risk factor for hepatocellular carcinoma. *J. Natl. Cancer Inst* 2012; **16**:104(10):790-792.
3. Bal?k I, Onul M, Tekeli E, Caredda F. Epidemiology and clinical outcome of hepatitis D virus infection in Turkey. *Eur J Epidemiol* 1991; **7**(1): 48-54.
4. Khalid M, Saeed SH, Salman A. et al. Epidemiology and clinical pattern of hepatitis delta virus infection in Pakistan. *J of Gastroenterology and Hepatology* 2005; **20**(10): 1503-1507.
5. Toy M, Önder FO, Wörmann T, Bozdayi AM, Schalm SW, Borsboom GJ, et al. Age- and region-specific hepatitis B prevalence in Turkey estimated using generalized linear mixed models: a systematic review. *BMC Infect Dis* 2011; **12**(11): 337.
6. Üner A, Kirimi E, Tuncer I, Ceylan A, Türkdogan M, Abuhandan M. Seroepidemiology of hepatitis B virus infection in children in the Eastern Anatolia. *East J Med* 2001; **6**(2):40-42.
7. Tabak F (Eds). Viral Hepatit. ?stanbul; Viral Hepatit Savasim Dernegi Press, 2007: 10-50.
8. Alizadeh AHM, Ranjbar M, Tehrani ASS, Keramat F, Mamani M, Rezazadeh M, et al. Seroprevalence of Hepatitis D Virus and its Risk Factors in the West of Iran. Journal of Microbiology, *Immunology and Infection* 2010; **43**(6): 519-523.
9. Karimi A, Amini Safieh AA. [Investigation and Comparison of hepatitis D prevalence in dialysis patients and the donors of HBsAg carrier]. *Teb va Tazkieh* 2000; **36**(30): 3.
10. Amini S, Mahmoodi MF, Andalibi S, Solati AA. Seroepidemiology of hepatitis B, delta and human immunodeficiency virus infections in Hamadan province, Iran: a population based study. *J trop med hyg* 1993; **96**(5): 277.
11. Roshandel G, Semnani S, Abdolahi N, Besharat S, Keshtkar AA, Joshaqani H, et al. Prevalence of hepatitis D virus infection in hepatitis B surface antigen-positive subjects in Golestan

province, northeast Iran. *J Microbiol Immunol Infect* 2008; **41**(3): 227-230.
12. Delic D, Gotic M, Ostric V, Fridman V, Nikolic P, Jemuovic L, et al. Epidemiology of hepatitis D virus (delta) infection in Yugoslavia. *Liver* 1993;**13**(6): 302-304.
13. de Miguel J, Collazos J, Mayo J, Lopez de Goicoechea MJ, Echaniz C, Mendarte U. Seroprevalence of delta virus and hepatitis C virus in patients with chronic infection with hepatitis B virus. *Rev Clin Esp* 1994; **194**(10): 897-900.
14. Chen CJ, Tseng SF, Lu CF, Lin HC, You SL, Chen CS, et al. Current seroepidemiology of hepatitis D virus infection among hepatitis B surface antigen carriers of general and high-risk populations in Taiwan. *J Med Virol* 1992; **38**(2): 97-101.
15. Munoz Espinosa LE, Ibarra Salas MJ. [Prevalence of hepatitis D in a population of Northeast Mexico and its relationship with other viruses]. *Rev Gastroenterol Mex* 1997; **62**(4): 246-249.
16. Zaki H, Darmstadt GL, Baten A, Ahsan CR, Saha SK. Seroepidemiology of hepatitis B and delta virus infections in Bangladesh. *J Trop Pediatr* 2003;**49**(6): 371-374.
17. Ivaniushina VA, Ryzhova EV, Grudinin MP, Katorgina LG, Nikonova AN, Vinogradova EN, et al. The frequency of antibodies against delta virus in patients with HBs positive hepatitis. *Vopr Virusol* 1996; **41**(4): 166-169.
18. Gaeta GB, Stroffolini T, Chiaramonte M, Ascione T, Stornaiuolo G, Lobello S, et al. Chronic hepatitis D: a vanishing Disease? An Italian multicenter study. *Hepatology* 2000; **32**(4): 824-827.
19. Bahcecioglu IH, Aygun C, Gozel N, Poyrazoglu OK, Bulut Y, Yalniz M. Prevalence of hepatitis delta virus (HDV) infection in chronic hepatitis B patients in eastern Turkey: still a serious problem to consider. *Journal of Viral Hepatitis* 2011; **18**(7): 518-524.
20. Celen MK, Ayaz C, Hosoglu S, Geyik MF, Ulug M. Anti-hepatitis delta virus seroprevalence and risk factors in patients with hepatitis B in Southeast Turkey. *Saudi Med J* 2006; **27**(5): 617-620.
21. Turkdogan MK, Bozkurt H, Uygan I et al. Chronic hepatitis delta virus infection in Van region of eastern Turkey. *Turk J Gastroenterol* 2005; **16**: 17-20.
22. Mansour W, Malick F-ZF, Sidiya A, Ishagh E, Chekaraou MA, Veillon P, et al. Prevalence, risk factors, and molecular epidemiology of hepatitis B and hepatitis delta virus in pregnant women and in patients in Mauritania. *Journal of Medical Virology* 2012; **84**(8): 1186-1198.
23. Mansour W, Bollahi M-A, Hamed C-T, Brichler S, Le Gal F, Ducancelle A, et al. Virological and epidemiological features of hepatitis delta infection among blood donors in Nouakchott, Mauritania. *Journal of Clinical Virology* 2012; **55**(1): 12-16.
24. Ouattara H, Siransy-Bogui L, Fretz C, Diane KM, Konate S, Koidio A, et al. Residual risk of HIV, HVB and HCV transmission by blood transfusion between 2002 and 2004 at the Abidjan National Blood Transfusion Center. *Transfus Clin Biol* 2006; **13**: 242-245.
25. Diarra A, Kouriba B, Baby M, Murphy E, Lefrere JJ. HIV, HCV, HBV and syphilis rate of positive donations among blood donations in Mali: lower rates among volunteer blood donors. *Transfus Clin Biol* 2009;**16**: 444-447.
26. Collenberg E, Ouedraogo T, Ganame J, Fickenscher H, Kynast-Wolf G, Becher H, et al. Seroprevalence of six different viruses among pregnant women and blood donors in rural and urban Burkina Faso: a comparative analysis. *J Med Virol* 2006;**78**: 683-692.
27. Ampofo W, Nii-Trebi N, Ansah J, Abe K, Naito H, Aidoo S, et al. Prevalence of blood-borne infectious diseases in blood donors in Ghana. *J Clin Microbiol* 2002; **40**: 3523-3525.
28. Toure-Fall AO, Dieye TN, Sall A, Diop M, Seck M, Diop S, et al. Residual risk of transmission of HIV and HBV, in Senegalese national blood bank from 2003 to 2005. *Transfus Clin Biol* 2009; **16**: 439-43.
29. Buseri FI, Muhibi MA, Jeremiah ZA. Sero-epidemiology of transfusion transmissible infectious diseases among blood donors in Osogbo, south-west Nigeria. *Blood Transfus* 2009; **7**:293-299.
30. Amini N, Alavian SM, Kabir A, Saiedi Hosseini SY, Aalaei Andabili SH. Clinical Features and Seroepidemiology of Anti-HDV Antibody in patients With Chronic Hepatitis B Virus Infection in Iran: A Meta-Analysis. *Hepat Mon* 2011; **11**(12): 960-967.
31. Romeo R, Del ninno e, Rumi M, Russo A, Sangiovanni A, de Franchis R, *et al*. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology* 2009; **136**(5): 1629-1638.