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 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%. 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.
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.

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 compiled 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 infection 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. Turkey is an intermede endemic area (2%-8%) for HBV infection. Turkey is divided into seven regions

<table>
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<th>Table 1. Distribution of anti-HDV (+) patients by age, gender, duration of HBsAg positivity, and the inhabited region.</th>
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<tr>
<td>Asymptomatic carrier (HBV)</td>
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<tr>
<td>Chronic active hepatitis B</td>
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<td>Duration of HBsAg positivity (&gt;5 years)</td>
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<tr>
<td>Age 34.5±15.1</td>
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<td>Gender (male)</td>
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<td>HBsAg (+) family member</td>
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<td>Living in Southeastern Anatolia</td>
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based on geographical characteristics and the prevalence of HBsAg varies by regions. In an Eastern Anatolia study, HBsAg prevalence was found to be 9.8% in men. In a study estimated overall population prevalence of HBV was 4.57, and total number of CHB cases was 3.3 million. 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. 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 prevalence of HDV is higher in eastern Europe and western Asia. The prevalence of HDV among HBsAg-positive individuals has been reported to be 1.5-5.8 in Iran, 1.5% in Yugoslavia, 1.6% in Spain, 2.2% in Taiwan, 4% in Mexico, 24.4% in Bangladesh, 12.5% in Russia, and 8.3% in Italy. In one of the Turkey studies, Bahçecioğlu et al found that 45% of chronic hepatitis B patients were positive for anti-HDV. In another study from Turkey, Çelen et al. found that 27.5% of chronic active hepatitis B patients was anti-HDV positive. 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 decrease 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. In current study and in Turkey studies, family history was found significantly higher among HDV-positive HBV patients when compared to negative ones. 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. 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.

On the other hand, it has been reported that phlebotomy, surgery, blood transfusions, and dental manipulations were the other risk factors for HDV positivity. Especially a high prevalence of HBsAg in blood donors has been described in several African countries and Sub-Saharan Africa: 8.65-44%. 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 occur during infancy or early childhood. 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.

In many Turkey studies and our study showed that HDV infection is more common in 35-45 years of age group but being male was found to be a risk factor for HDV seroprevalence. 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 treatments, etc.), were generally living in communities. 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. In some studies HBsAg levels were also found to be higher in HDV-RNA-positive patients. These studies suggested that elevated HBsAg levels rather than HBV DNA levels can provide evidence for HDV replication in patients with chronic HDV. Celen et al found that the prevalence of anti-HDV in asymptomatic hepatitis B carriers was 6% and in chronic active hepatitis B patients 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. 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. 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. As a result we can say that elevated HBsAg levels lead 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. However in some studies, any association with HBeAg positivity and anti-HDV positivity was not found. 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 early 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


