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The Evaluation of Exposure to Hepatitis A Virus in HBsAg-positive Persons : A Multicentre Study from Turkey

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Chronic hepatitis B is a major public health problem in our country. Hepatitis A vaccination in HBV carriers who did not encounter with Hepatitis A virus is also significant. We aimed to evaluate the rate of exposure to HAV in HBsAg-positive persons, and the distribution of seronegative individuals according to age groups. Medical records of 4793 patients from 14 centers who were positive for hepatitis B surface antigen (HBsAg). A total 3514 cases (73.3%) were male and 1279 (26.7) were female. The HBsAg positive patients who were previously tested for HAV IgG at the time of firstly admitted to a center. HBsAg positive patients who were previously not tested for HAV IgG were tested and these patients were confirmed serologically for HAV. The distribution of cases according to age were determined. In this study, 4793 HBsAg-positive patients were evaluated. The ratio of testing of anti-HAV IgG was very low during the first visit (54.2%). Seronegativity was highest in the age group under 19 years of age (26.2%) followed by 20-25 age group (15.5%) and 26-29 age group (12.5%). Testing of HAV serology should not be ignored in especially HBsAg-positive young adults and seronegative young adults should be vaccinated.

Key words: Hepatitis A, HBsAg, anti-HAV IgG.

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Hepatitis A virus (HAV) is a non-enveloped single-stranded RNA virus which replicates in hepatocytes and interferes with liver function and led to liver inflammation and acute hepatitis A infection. Hepatit A virus is acquired by the fecal-oral route[1,2].

Approximately 1.5 million clinical cases of hepatitis A occur worldwide per year. The incidence of HAV in Turkey in 2007 was 11/100 000 and in 2008 was 9.8/100 000 (3). Incidence of this infection is related to socioeconomic indicators and access to safe drinking water[1]. Risk factors for hepatitis A are close personal contact with an infected person, men who have sex with men, travel to endemic regions, illicit drug use, food-borne outbreak, and contact with a child or employee in a child care center[4].

This infectious disease is generally self-limited and asymptomatic in chilhood. However in the big majority of adults, Hepatitis A led to clinically apparent disease and may progress to fulminant hepatic failure. Currently, especially in developing countries pattern of acute hepatitis A infection changed with a transition from asymptomatic childhood infections to a symptomatic disease and fulminant liver failure in young people and adults[5-7].

Chronic liver disease (CLD) (e.g. chronic hepatitis B, chronic hepatitis C) and old age are considered to be among the risk factors for fulminant liver failure in Hepatitis A patients[2]. Hepatitis B infection is an important cause of CLD in Turkey and a large-scale study investigating the prevalence of HAV in HBeAg-positive patients has not been perform in Turkey. For this purpose, in this study, we aimed to evaluate the rate of exposure to HAV in HBsAg-positive persons, and the distribution of age groups in HAV seronegative individuals. In addition with present multi-centre study, we aimed to provide the objective data about the HAV vaccination strategy in HBsAg-positive patients.

MATERIALS AND METHODS

We retrospectively analyzed the medical records of 4793 patients from 14 centers who were positive for hepatitis B surface antigen (HBsAg). A total 3514 cases (73.3%) were male and 1279 (26.7) were female. A distinction did not perform in terms of inactive HBsAg carrier or Chronic hepatitis B among patients. In this study all patients were included in the HEP-NET (The Hepatitis Information Network) patient monitoring program. The anti-hepatitis C virus antibody (anti-HCV) positive patients and the patients with liver cirrhosis or hepatocellular carcinoma were excluded. The HBsAg-positive patients who were previously tested for HAV IgG at the time of firstly admitted to a center were recorded and these patients were confirmed serologically for HAV. In the HBsAg- positive patients who were previously not tested for HAV IgG were tested and seroprevalence of IgG anti-HAV was investigated. HAV IgG test results obtained from the study of patients were recorded in the computer environment. In this study the distribution of cases according to age were also determined and evaluated (Table I). ELISA-based commercial kits used for serological tests. Ethics committee approval was obtained for this study.

RESULTS

In this multi-center participated retrospective study, 4793 HBsAg-positive patients were evaluated. A questionnaire was completed for each patient and the patients' demographic,

Table 1. HAV IgG results of HBsAg-positive persons and the distribution according to age groups

Age groups	HAV IgG positive	HAV IgG negative	Total
<19	203 (%73.8)	72 (%26.2)	275
20-25	545 (%84.5)	100 (%15.5)	645
26-29	596 (%87.5)	85 (%12.5)	681
30-35	712 (%95.8)	30 (%4.2)	742
36-44	928 (%98.3)	16 (%1.7)	944
45-64	1256 (%99.5)	7 (%0.5)	1263
65 +	243 (%100)	0 (%0)	243
Total	4483 (%93.5)	310 (%6.5)	4793

aetiological and clinical data were recorded from the 14 centers including the following different regions Diyarbak1r, 0stanbul (two centers), Antalya, Çanakkale, Sakarya, Nev_ehir, Tekirda, Düzce,Van, Bolu, Isparta, Bingöl, Manisa. The mean age of male was 38.5 ± 23.9 and the mean age of the female was 34.9 ± 2.25. Mean duration of HBsAg-positivity was 9.1 ± 3.7 months in HBV carriers. Mean duration of HBsAg-positivity in patients with chronic HBV was 12.8 ± 7.1 months. The ratio of testing of anti-HAV IgG during the first visit was %54.2 and before the first visit was 22.8%. Hepatitis A seronegativity was highest in the age group under 19 years of age (26.2%) followed by 20-25 age group (15.5%) and 26-29 age group (12.5%) (Table I).

DISCUSSION

Hepatitis A is one of the major causes of acute viral hepatitis worldwide. This infectious disease is generally self-limited and asymptomatic in chilhood. However in recent years acute hepatitis A infection pattern changed with a transition from asymptomatic childhood infections to a symptomatic disease and fulminant liver failure in young people and adults[5-7]. Therefore, vaccination of hepatitis A in the general population gained importance, currently. Previously, Hepatitis A virus vaccine was not routinely used in our country. It was known that there were some individuals who had escaped exposure to Hepatitis A in community.

According to literature, the development of hepatitis A infection in patients with chronic liver disease (e.g. chronic hepatitis B, chronic hepatitis C) has negative effects on the course of disease[2]. As is known, Hepatitis B infection is a viral cause of chronic liver disease. For this reason, screening for the Hepatitis A virus and prevention of hepatitis A super-infection in HBsAg-positive patients, has a great importance. Hepatitis A virus is a single serotype of the disease, and IgG antibodies remain positive for life. Due to screening of anti-HAV IgG is a commonly used and reliable method, we used this method in current study.

World Health Organization (WHO) was characterized areas of the world as having high, intermediate and low endemicity for hepatitis A. Less developed countries (Africa, Asia and Central and South America) with poor sanitary and hygienic conditions, is highly endemic for HAV infection. In this regions most of the persons become infected in early childhood and HAV infection is often asymptomatic[1]. However particularly in developing countries and some developed countries, sanitary and hygienic conditions can vary according to the regions and some of the children can avoid infection. The peak rates of infection commonly occur in later childhood or adolescence and wide epidemics may occured in these regions[1,8,9]. In developed countries (such as North America, Western Europe, Australia and Japan) that sanitation and hygienic conditions are generally good, infection rates in children are generally low. Reported diseases and peak rates of infection can be observed among adolescents and young adults in these areas[10,11]. Turkey is a developing country and an intermediate endemic area for Hepatitis A. In some provinces of our country the epidemiological pattern of HAV infection has been changed and disease severity has been gradually increased due to an improved socioeconomic status, more sanitary conditions and better hygiene practice. In Turkey, in various studies, the rate of HAV infection among children was found to be 35-80% [12-20]. In other words, we can say that 20%-65% of adults are susceptible to HAV infection in Turkey. In a multi-centre Turkey study among children and adolescents 44.65% (623/1395) was HAV IgG pozitif. According to Turkey study, 23.4% of 15-17 age group has not been exposed to Hepatitis A, previously[21]. These studies demonstrated that individuals who have not yet met with Hepatitis A in our country should not be ignored.

The studies have showed that the clinical course of HAV infection is more severe in patients with Hepatitis B[22,23]. Prevalence of hepatitis B was reported as 6 % in a multi-center Turkey study and this rate may exceed 20 percent in some areas[24]. Therefore Hepatitis B is a significant public health problem for our country. In an outbreak of HAV infection, mortality of HBsAg positive patients was found to be significantly higher than HBsAg negative patients[25]. A United States study also showed that HAV associated deaths revealed a higher rate of fatality in HBV carriers than in patients without HBV[26]. For this reasons, investigation of HAV seopositivity in HBsAg

positive patient have important roles for providing the objective data about the HAV vaccination strategy and preventing of Hepatitis A infection in HBsAg positive patients.

In literature there were a few studies evaluating the HAV seropositivity in HBsAg positive patients. Among three Koraen studies, in first 986 patients study the overall seroprevalence of IgG anti-HAV in patients with chronic viral liver disease was found to be 86.61%. The anti-HAV seroprevalence was 6.67%, 50.86%, 92.29%, 97.77% and 100% in patients in their 20s, 30s, 40s, 50s and 60s, respectively[22]. In second study the seroprevalences of IgG anti-HAV were investigated among 419 Hepatitis B patients and 23.1% of patient was between 26 and 30 years old, 64% was 31-35 years old, 85.0% was 36 and 40 years old[27]. In third study the patients were categorized by decade of age (teens, 20s, 30s, 40s, 50s, >60) and the overall seroprevalence of anti-HAV was 87.8%. The seroprevalence in each age group was 22.2, 26.1, 72.2, 97.4, 100 and 98.8%, respectively, showing marked increase in those over 40 years of age[28].

A multi-centre study with 2830 patient was performed in Italy[29]. Antibody to HAV was detected in 53.5% of the patients; Both in central and southern Italy the prevalence of anti-HAV positive patients increased with increasing age from 43.3 and 44.7%, respectively, in the 0-30-year-old patients to 80.1 and 68.3%, respectively, in those aged over 60 years. The overall prevalence was much lower in northern Italy, as were the variations from one age group to another, from 28.4% in the 0-30-year-old patients to 38% in those aged over 60 years[29].

Our study of 4793 patient is the only large-scale study that investigates HAV seropositivity in HBsAg-positive cases and evaluates the distribution patients according to the age groups. Seronegativity was highest in the age group under 19 years of age (26.2%) followed by 20-25 age group (15.5%) and 26-29 age group (12.5%). The results of current study were consistent with other studies. Our data indicated that the big majority of HBsAg positivite-patients and who are above 45 years of age have already been exposed to HAV infection, and have naturally acquired immunity against HAV. We found that exposure to Hepatitis A in patients <19 years was in substantial rate. In light of these data, we can say that HBsAg-positive young adults should be vaccinated for Hepatitis A.

On the other hand, we found that the testing ratio of anti-HAV IgG in HBsAg-positive patients was very low at the time of firstly admitted a center. We suggested that testing of HAV serology should not be ignored in especially young adult age group for early vaccination.

In current study the overall prevalance of HAV IgG in HBsAg positive patients were 93.5%. This rate is higher than other studies. However there was no data related to a high incidence of HAV in HBsAg-positive individuals. In our study we did not test anti-HAV IgM positivity in healthy subjects. Cho et all. found no statistically significant difference in anti-HAV seroprevalence between the healthy people and HBsAg positive patient (86.61% vs 88.13%, respectively) [22]. They suggested that the immune response to HAV infection is not altered by chronic infection with HBV[22]. The reason of high rates may be the vast majority of cases have poor living conditions.

Another point which should not be overlooked was patients with chronic hepatitis or cirrhosis may lack naturally acquired immunity to HAV[29]. In addition the overall seroconversion rate of IgG in chronic liver disease after recommended two doses of Hepatitis A vaccine was found to be 86.17% in a study[22]. Therefore we can say that vaccination is very important in young inactive HBsAg carriers.

The relationship between gender and HAV prevalence in HBsAg-positive individuals varies by region. Kim *et al*. observed no difference in sex of two groups of patients[28]. Sagnelli *et al*. reported that HAV prevalence was higher in females[29]. They thought that big majority of females were housewife in developing countries. These females with low socio-cultural level have many social and household contacts and so probably have more exposure to HAV. Due to majority of our cases were male, we can not go a distinction in this regard.

In conclusion, our study showed that most HBsAg positive patients who are above 45 years of age have already been exposed to HAV. However exposure to Hepatitis A of patients <19 years was in substantial rate. In addition our study revealed that testing of HAV serology should not be ignored in especially young adult age group for

early Hepatitis A vaccination in our country. HBsAg-positive young adults should be tested for HAV during the first admission to a center and should be vaccinated. With the new regulations in our country, patients with chronic hepatitis infection can receive two doses of HAV vaccines for free. We thought that this implementation will be beneficial for public health.

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