International Journal of Medical Science and Clinical Research
www.journalofmedical.com
Online-ISSN: 2664-7761, Print ISSN: 2664-7753
Received: 02-02-2022, Accepted: 17-02-2022, Published: 04-03-2022
Volume 4, Issue 1, 2022, Page No. 15-19

Investigation of anti-HAV IgG seropositivity in HBsAg positive patients

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Abstract
Objective: Although hepatitis A virus (HAV) infection is a disease with mild symptoms and good prognosis it may be more severe and even fatal if it develops with a chronic liver disease such as chronic hepatitis B. Therefore, it is important to have information about anti-HAV IgG seroprevalence in patients with chronic hepatitis B.
Material and Methods: A total of 156 patients who were diagnosed with chronic hepatitis B infection and who were asked for anti-HAV immunoglobulin G (IgG) test were included in the study. In serum samples, hepatitis B surface antigen (HBsAg) and anti-HAV IgG tests were analyzed using enzyme immunoassay technique.
Results: Ages of the patients included in the study ranged from 7 to 88 and 88 (56.4%) of them were male. Anti-HAV IgG seropositivity was detected in 95.5% of the patients. Seropositivity rates were 95.8%, 98%, and 93% in <30, 30-50 and> 50 years old groups, respectively. While anti-HAV IgG positivity was the highest in the age groups of <30 and 30-50 in males with a rate of 100%, it was the highest in the age group of 30-50 in females with a rate of 96.2%.
Conclusions: Anti-HAV IgG positivity was detected in 95.5% of the study group and it was concluded that 4.5% of the patients needed vaccination to prevent HAV infection. Investigation of hepatitis A immunization status in patients with other life-threatening chronic liver diseases in addition to chronic hepatitis B virus infection and vaccination of anti-HAV IgG negative patients are recommended.

Keywords: Hepatitis a virus, anti-HAV IgG, chronic hepatitis b, seropositivity

Introduction

Hepatitis B virus (HBV) is a tiny enveloped virus and a prototype of the family *Hepadnaviridae* [1]. The World Health Organization predicts that 257 million individuals lived with chronic hepatitis B infection in 2015 and that 887 thousand of these patients died due to primary liver disease in the same year [2]. HBV, which can cause acute and chronic infection, cirrhosis, and liver cancer, is a global health problem [3]. Global prevalence of HBV is predicted to be 3.9% [4]. HBV infection is also an important health problem in Turkey like in the world. The estimated number of individuals with HBV in Turkey is about 3.3 million and the general prevalence is 4.57% [5].

Hepatitis A infection is the most common worldwide acute viral hepatitis form caused by Hepatitis A virus (HAV) [6]. HAV is a non-enveloped, single-stranded, positive sense, and linear RNA virus, which is a member of the *Hepatovirus* genus of the family *Picornaviridae* [7]. HAV transmission usually occurs through the fecal-oral route and person-to-person contact [8]. Infection rate is closely related to the access to safe drinking water and socioeconomic status. Globally, high-income regions have low HAV endemicity (less than 50% of the population) while low-income regions have a high endemicity (more than 90% of the population) [2, 9].

HAV infection shows high prevalence, especially in sub-Saharan Africa, India, Pakistan and Afghanistan, whereas in Central and South America, North Africa, Middle East, Turkey, Iran, Kazakhstan and Mongolia shows the low prevalence [10]. Almost all children in endemic countries become infected at an early age, many of which are asymptomatic but acquire lifelong immunity. Paradoxically, patients are prone to symptomatic infection in low endemic countries and the disease has a more severe course [11].

Anti-HAV seropositivity in Turkey differs according to the geographical regions, socioeconomic status and age. Our country is in a moderately endemic region with an anti-HAV seropositivity rate of 80% in adult age group and 20% in those under 10 years old [12]. These data are related to the statistics before 2010 and the hepatitis A vaccine program started after 2012 in our country.

Chronic HBV infection is still one of the most important agents of chronic liver disease although vaccination has been initiated. Therefore, anti-HAV seroprevalence has a great importance in this kind of patients. While HAV infection has a very mild course and a good prognosis it may become a disease causing severe course, even decompensation and death in the presence of a disease causing liver damage [13-15]. The data obtained from a

great acute hepatitis A outbreak in Shanghai in 1988 and hepatitis A cases reported to the Center for Disease Control and Prevention (CDC) between 1983 and 1988 revealed that HAV infection was more severe in patients with previous chronic liver disease [16, 17]. These observations led to having knowledge of hepatitis A seroprevalence and recommending vaccines for seronegative patients in chronic liver patients including chronic hepatitis B virus infection[18, 19].

This study aimed to assess hepatitis A serology of hepatitis B surface antigen (HBsAg) positive patients to obtain data about HAV vaccination need in these patients and determine the distribution of seronegative cases according to the age groups.

Materials and Methods

Patients with chronic HBV infection who were tested for anti-HAV immunoglobulin G (IgG) between the 1st of January 2017 and 31st of December 2019 in the Serology Laboratory of the Microbiology Department of the University of Health Sciences, Gulhane Training and Research Hospital were included in this study.

Patients from all age groups who were Turkish citizens, who were not Turkish citizens but lived in Turkey and whose test results were sent to our laboratory between 2017 and 2019 were included in our study. Female, male or pediatric patients whose hepatitis B surface antigen (HBsAg) and anti-HAV IgG results, did not cover the planned years were excluded from the study. Duplicate or erroneous reports were also excluded.

HBsAg and anti-HAV IgG tests in serum samples were performed using Architect HBsAg, anti-HAV IgG reagent kits (Abbott, Germany) with chemilumine scence enzyme immunoassay (CLIA) technique on Architect i2000SR system (Abbott, USA). Tests were qualitatively analyzed according to the instructions of the manufacturer. Architect CLIA system measures the sample to cut-off (S/CO) ratio. For HBsAg and anti-HAV IgG tests, if the S/CO value is <1.0, it is accepted as non-reactive and ≥1 as reactive.

Ethical approval

Ethical approval was obtained from the Non-Interventional Research Ethics Committee of the University of Health Sciences Gulhane Training and Research Hospital (reference number: 2020/19/418).

Statistical analysis

SPSS 22 (IBM Corp.) software program was used for statistical analysis of the data obtained from the study. Whether the variables were normally distributed or not was assessed with visual methods (histogram and probability plots) and Kolmogorov-Smirnov test. Variables were compared using Student's t-test or Mann-Whitney U test. Pearson chi-square tests or Fisher's exact test were used for qualitative variables. *P* values under 0.05 were accepted as statistically significant results.

Results

A total of HBsAg positive 156 patients (Male:Female ratio 1.3:1) who were tested for anti-HAV IgG and diagnosed with chronic Hepatitis B between the 1st of January 2017 and 31st of December 2019 were included in the study. Anti-HAV IgG seropositivity status in HBsAg positive patients were given in Table 1. Of the patients whose ages ranged from 7 to 88, 88 (56.4%) were male and 68 (43.6%) were female patients. Median age of the study group was 41 years and while median age of male patients was 42 years (range: 8-88) that of female patients was 41 years (range = 7-76) (p = 0.60).

Table 1. Anti-HAV IgG seropositivity status in HBsAg positive patients

Gender	HBsAg Positive n	Anti-HAV IgG		p - value
		Negative n (%)	Positive n (%)	
Male	88	3 (3.4)	85 (96.6)	0.70
Female	68	4 (5.9)	64 (94.1)	
Age groups (year)				
< 30	48	2 (4.2)	46 (95.8)	0.50
30-50	51	1 (2)	50 (98)	
> 50	57	4 (7)	53 (93)	
n, number				

Anti-HAV IgG seropositivity was detected in 95.5% (149/156) of the patients. Seropositivity rate was 96.6% (85/88) in male patients and 94.1% (64/68) in female patients (p = 0.70).

Anti-HAV IgG seropositivity rates in <30, 30-50 and >50 age groups were 95.8% (46/48), 98% (50/51) and 93% (53/57), respectively (p = 0.50). Anti-HAV IgG was positive in all patients under 25 years of age. Anti-HAV IgG positivity rate was the highest (100%) in <30 and 30-50 age groups in male patients, while it was the highest (96.2%) in the 30-50 age group in female patients (p = 0.11 and p = 0.67, respectively) (Figure 1).

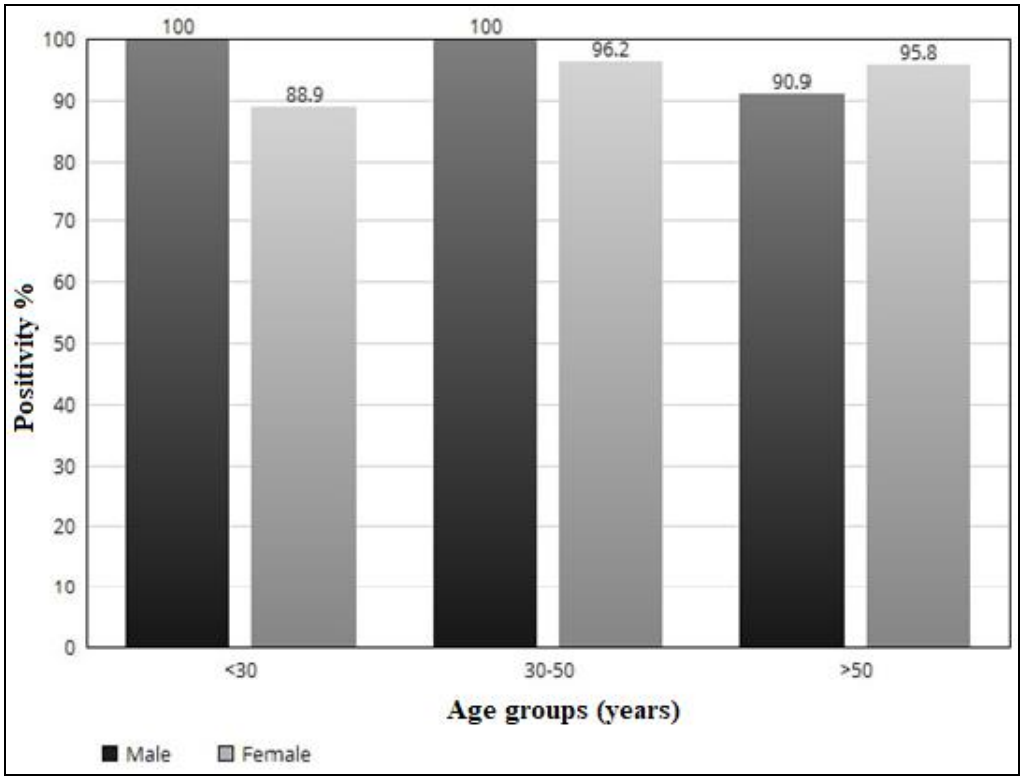

Fig 1: Anti-HAV IgG positivity rates in different age groups in male and female patients

Discussion

Clinical spectrum of HAV infection ranges from asymptomatic infection to fulminant hepatitis. Clinical symptoms are associated with the age of the host. Less than 30% of the little children infected with HAV and approximately 80% of adults are symptomatic.[20] Serological tests used for diagnosis were developed in the 1970s and HAV was first isolated in 1979. Hepatitis A vaccines developed for protection from the disease were licensed in 1995 and 1996 [21].

Our country is endemic for HAV, but its frequency is gradually decreasing and the age of exposure to the virus changes towards adolescents and young adults. Hepatitis A vaccine, which has been included in the childhood vaccination calendar since the end of 2012 in our country, is administered to children at the 18th and 24th months as two doses [22].

Viral hepatitis co-infection is a cause of increased morbidity, especially in individuals with chronic liver disease [23]. The Advisory Committee on Immunization Practices approved Hepatitis B vaccine for all patients with Hepatitis C virus (HCV) infection and that vaccination against HAV must specially be considered for individuals with HBV and HCV infections [24, 25].

Anti-HAV IgG positivity in patients with chronic liver disease was reported between 77% and 100% in different regions of Turkey [26-32]. The lowest HAV IgG positivity was reported in Balikesir (77%) and the highest seropositivity was reported in patients with chronic HDV infection in Ankara (100%) [26-32]. In this study, 95.5% of the patients who were diagnosed with chronic HBV were anti-HAV IgG positive. This is the highest rate of Seropositivity compared to similar studies conducted in our country. There was no significant difference in anti-HAV IgG positivity rates in different age groups and gender. When other studies are evaluated, this supports the fact that factors such as education, hygiene and sanitation conditions, crowded life, and improved living standards may affect regional difference in seropositivity rates [26-33]. Of the patients diagnosed with chronic HBV, 4.5% were found to be sensitive to HAV.

In different studies evaluating seropositivity rates according to age groups, the lowest seropositivity was found under the age of 20, and it was reported that seropositivity rates increased with increasing age [26-28]. In our study, all the patients under the age of 25 had interestingly anti-HAV IgG seropositivity. This seropositivity rate can be explained by hepatitis A prophylaxis of the patients or previous HAV infection they had. In Turkey, it has been included in the childhood vaccination calendar at the end of 2012, and it is administered to children born on March 1, 2011 and later, in 2 doses, at the end of 18 and 24 months. However, the vaccine is administered free of charge to people in the risk group (chronic hepatitis B and hepatitis C patients, etc.) [22]. Hepatitis A vaccine is recommended for the risk groups such as intravenous drug users, homosexuals and patients with chronic liver disease [21].

In studies on hepatitis A seropositivity in Turkey, hepatitis A seropositivity showed regional difference [34-40]. Western and Middle Anatolia regions show middle endemicity and the Eastern Anatolia region is still highly endemic for HAV. Vaccination measures depend on endemicity. Including the vaccine in the childhood vaccination program in Turkey aims to prevent the disease to occur in more advanced ages [40].

The most important aspect of this study is to determine the anti-HAV IgG status of 156 HBsAg positive patients admitted to the hospital and to determine the vaccination needs of the negative patients. Because HAV infection in chronic hepatitis B patients has a more severe clinical course and a higher mortality rate than in healthy individuals. In our study, seven HBsAg positive and anti-HAV IgG negative patients were determined to be in need of vaccination. In this way, a decrease in the severity of clinical course and even death rate of hepatitis A infection on the background of hepatitis B virus infection will be ensured. In addition, it was determined that the incidence of acute hepatitis A decreased compared to previous years. Although this difference is thought to be due to the increase in compliance with the rules of cleanliness and hygiene in our country, increase in access to clean water resources and the improvement of socioeconomic conditions, Hepatitis A virus infection is still endemic in the environment.

This study has some limitations. As it was a laboratory-based retrospective study hepatitis A vaccine history of the patients could not be questioned. Body mass index, pregnancy, diabetes or obesity status could not be evaluated. Clinical diagnoses of the patients were assessed from the information system. The data should not be interpreted for the general population in Ankara as the number of patients was low and the data of a single hospital were included.

Conclusion

This study aimed to determine the seroprevalence of anti-HAV IgG in patients who were followed up for chronic HBV infection in our hospital and the need for vaccine in this patient group. In the study group, 95.5% were anti-HAV IgG positive. Accordingly, it was determined that 4.5% of the patients needed vaccination to prevent HAV infection. Investigation of the status of immunization against HAV in patients with other chronic liver diseases threatening the life as well as chronic HBV infection and vaccination of anti-HAV IgG negative patients are recommended.

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