

Hepatitis A seroprevalence in patients with chronic viral hepatitis in Konya, Turkey

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Aim Hepatitis A is among the diseases that can be prevented with vaccination in our time. Acute hepatitis A progresses more severely in individuals with a liver disease. Therefore, patients with a chronic liver disease (because of hepatitis B or hepatitis C) are advised vaccination with the hepatitis A vaccine. This study is aimed to determine the seroprevalence of hepatitis A virus (HAV) antibodies in patients infected with hepatitis C virus or hepatitis B virus in Konya province of Turkey.

Methods A total of 537 patients who had chronic viral hepatitis between January 2011 and December 2014 were included in the study. Serum samples were collected from each patient and tested for anti-HAV using the chemiluminescent microparticle immunoassay.

Results The overall seroprevalence of total anti-HAV IgG was 94.2%. The overall prevalence of anti-HAV IgG in patients with chronic hepatitis B virus and hepatitis C virus infection was 97.5 and 93.6%, respectively. Anti-HAV IgG positivity was 97.4% in cirrhotic patients and 93.9% in noncirrhotic individuals.

Conclusion At the end of the study, being older than 40 years and living in a rural area were found to be independent risk factors for anti-HAV IgG seropositivity. In conclusion, we recommend that patients younger than 40 years and/or those living in cities and having a chronic liver disease should be vaccinated with the hepatitis A vaccine. *Eur J Gastroenterol Hepatol* 28:333–337

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Introduction

Acute viral hepatitis A, which is caused by the hepatitis A virus (HAV), is an infectious disease that is prevalent worldwide, but more in underdeveloped and developing countries, and which can be prevented through vaccination. It is the most common cause of hepatitis worldwide [1]. Although it is usually asymptomatic and subclinical in children, it can appear in a variety of clinical forms ranging from a mild flu-like condition to a fulminant hepatitis [2]. A severe disease and fulminant liver failure because of HAV may occur in adulthood or in the elderly population and in patients with chronic liver disease (CLD) [3].

Although the seroprevalence of anti-HAV IgG has decreased in many countries, it is still quite high in underdeveloped countries [4]. The HAV seroprevalence is known to increase as much as 100% before 10 years of age in regions with a high endemicity, whereas in regions with moderate and low endemicity, this rate is around 10%

until mid-adolescence [5]. Turkey is in the moderately endemic group in terms of the epidemiology of HAV infection. The most recent data show that the HAV is still widely circulating endemically in our country, but the age of encountering the virus shifts towards adolescence and young adulthood particularly in the Western Anatolia region of our country and in other regions of higher socioeconomic level [6]. Decreasing hepatitis A incidence in line with accelerating development in our country makes vaccination against HAV more important in CLD patients who are at risk. Clean water and food, adherence to personal hygiene practices, and vaccination with the hepatitis A vaccine are important for protection from hepatitis A infection.

Konya is a province located in the Central Anatolia region of our country. Its socioeconomic status is better compared with the provinces in Eastern Anatolia and moderate compared with the provinces in Western Anatolia. The present study explores the rates of exposure to HAV by age groups and the need for vaccination in patients being monitored for chronic viral hepatitis diagnosis in our province.

Materials and methods

We included 537 individuals in our study who presented between January 2011 and December 2014 to the Infectious Diseases and Clinical Microbiology Outpatient Clinic of Baskent University Konya Medical and Research Hospital and who were diagnosed with chronic hepatitis B or chronic hepatitis C and/or liver cirrhosis. Patients whose hepatitis B surface antigen (HBsAg) was positive for 6 months and those whose hepatitis C virus antibody (anti-HCV) and HCV-RNA value were positive twice within an

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interval of at least 6 months were enrolled in the study. Patients who had received the hepatitis A vaccine previously and those who had nonviral or autoimmune hepatitis were excluded from the study. The status of underlying liver disease was classified into chronic hepatitis and liver cirrhosis. The diagnosis of liver cirrhosis was made if any one of the following findings was encountered: (i) compatible intraoperative gross findings or histologically compatible findings; (ii) evidence of portal hypertension in patients with liver disease; and (iii) compatible radiologic findings and platelet counts less than 100 000/mm³.

Blood samples of 10 ml were obtained from each patient. The samples were analyzed for the HBsAg, anti-HCV, and anti-HAV IgG parameters using the chemiluminescent microparticle immunoassay method in line with the procedure suggested by the manufacturing company (Architect i2000; Abbott Diagnostics, Abbott Park, Illinois, USA). Recurrent reactive results were considered positive. HCV-RNA detection in serum samples was performed using real-time PCR with a commercial kit (Fluorion; Iontek, Istanbul, Turkey). For RNA extraction, the QIAamp, Viral RNA Mini Extraction Kit (Qiagen, Hilden, Germany) was used in accordance with the instructions of the manufacturer.

The distribution of the patients by age and sex was assessed. The patients were divided into age groups of 10 years each.

Statistical analysis

The data were statistically analyzed using the SPSS (version 15.0; SPSS Inc., Chicago, Illinois, USA) statistical program. The data were described as numbers, percentages, and mean \pm SD. The χ^2 -test was used for qualitative changes and Student's *t*-test, one-way ANOVA, and variance analysis were used for quantitative changes when assessing the data. A χ^2 -test was used to determine whether significant differences existed between two categorical variables. For multivariate analyses, a stepwise multivariate logistic regression model was used to assess the relative importance of variables showing a significant association ($P < 0.05$). The results of all multivariable analyses were reported as adjusted odds ratio, 95% confidence interval, and exact *P* value.

Results

A total of 537 patients were included in the study. A total of 437 patients were diagnosed with chronic hepatitis B, 60 with chronic hepatitis C, 18 with liver cirrhosis associated with chronic hepatitis B, and 22 with liver cirrhosis associated with chronic hepatitis C. A total of 297 (55.3%) of the patients were men and 240 (44.7%) were women. Their mean age was 45.9 \pm 14 years (15–81 years). Anti-HAV IgG was found to be positive in 506 (94.2%) patients and negative in 31 (5.8%) patients. The demographic characteristics of the patients are shown in Table 1.

When the study participants were classified by decade of age into seven groups, from less than 20 years to older than 70 years old, most of the chronic hepatitis patients were found to be in the 51–60 age interval and 64.6% of

Table 1. Patients' characteristics

	N (%)
Age [mean (range)] (years)	45.9 \pm 14 (15–81)
Sex	
Female	240 (44.7)
Male	297 (55.3)
Etiology of liver disease	
Chronic viral hepatitis B	437 (81.4)
Chronic viral hepatitis C	60 (11.2)
HBV-related liver cirrhosis	18 (3.4)
HCV-related liver cirrhosis	22 (4)
Place of residence	
City	302 (56.3)
Town	194 (36.1)
Rural area	41 (7.6)
Prevalence of IgG HAV	506 (94.2)

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

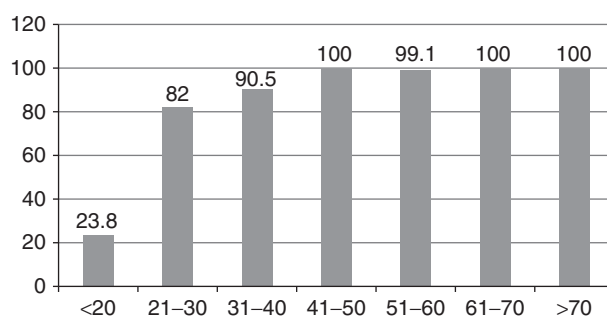


Fig. 1. Prevalence of IgG anti-hepatitis A virus according to age in patients with chronic viral liver disease.

Table 2. Prevalence of IgG anti-hepatitis A virus in patients with hepatitis B versus those with hepatitis C virus infection [n (%)]

Age (years)	Anti-HAV/HBV	Anti-HAV/HCV
< 20	5/21 (23.8)	0
21–30	64/77 (83.2)	0/1 (0)
31–40	92/102 (90.2)	2/3 (66.7)
41–50	110/110 (100)	4/4 (100)
51–60	92/93 (98.9)	30/30 (100)
61–70	46/46 (100)	31/31 (100)
> 70	6/6 (100)	13/13 (100)

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

them were 40 years of age and older. Anti-HAV IgG seropositivity was 23.8% in the age group younger than 20 years, 82% in the 21–30 age group, and 90.5% in the 31–40 age group. The positivity rate for anti-HAV in the patients in their 40, 50, 60s, and those older than 71 years was 100, 99.1, 100, and 100%, respectively (Fig. 1). Anti-HAV IgG seropositivity in chronic hepatitis B and chronic hepatitis C patients is shown in Table 2 by age groups. The anti-HAV seroprevalence was significantly higher in patients older than 40 years compared with those patients younger than 40 years of age (99.7 vs. 80.4%, respectively, $P < 0.05$) (Table 3).

Anti-HAV IgG seropositivity was found in 94.3% of male patients and 94.2% in female patients, and the difference was not statistically significant ($P > 0.05$; Table 3). With respect to the etiology of liver disease and the status of liver disease, anti-HAV IgG was positive in 93.6% of the chronic hepatitis B patients and in 97.5% of the

Table 3. Factors affecting seropositivity for IgG anti-hepatitis A virus in the multivariate analysis

Characteristics	Anti-HAV IgG positivity [<i>n</i> (%)]	OR (95% CI)	<i>P</i> value
Age (≥ 40 years)	346/347 (99.7)	64.87 (8.8–480)	< 0.05
Sex		0.98 (0.47–2.03)	> 0.05
Female	280/297 (94.3)		
Male	226/240 (94.2)		
Etiology of liver disease		0.37 (0.09–1.57)	> 0.05
HBV	426/455 (93.6)		
HCV	80/82 (97.5)		
Status of liver disease		0.42 (0.06–3.2)	> 0.05
Chronic viral hepatitis	469/499 (93.9)		
Liver cirrhosis	37/38 (97.4)		
Place of residence			< 0.05
City	238/260 (91.5)		
Town	154/161 (95.6)		
Rural area	34/34 (100)		

Bold font indicates statistical significance.

CI, confidence interval; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio.

chronic hepatitis C patients ($P > 0.05$). Anti-HAV IgG positivity was found to be 97.4% in cirrhotic patients and 93.9% in noncirrhotic patients, the difference being statistically insignificant (Table 3).

With respect to the residences of the patients with chronic viral hepatitis, anti-HAV IgG positivity was found to be significantly higher in those living in rural areas than in patients living in cities ($P < 0.05$; Table 3).

Multivariable analysis of the factors for anti-HAV seropositivity is shown in Table 3. At the end of the study, being older than 40 years and living in a rural area were found to be independent risk factors for anti-HAV IgG seropositivity.

Two doses (at months 0 and 6) of the hepatitis A vaccine were administered to 21 of the 31 patients who had been found to be anti-HAV IgG negative. Only eight of these 21 patients could be examined for the outcome and anti-HAV IgG was found to be positive in all of them.

Discussion

Developing countries are currently facing a change in the epidemiological pattern of HAV infection. Improved socioeconomic statuses, more sanitary environments, and advanced hygienic practices all play a role in steadily reducing the incidence of HAV infection and age-specific HAV seroprevalence in the general population. Declining HAV infections particularly in young adults have led to a decrease in the number of individuals with protective antibodies, resulting in an increase in the prevalence of hepatitis A in this population [7]. With the improvements in the sanitation and hygiene conditions in our country in recent years, the age of exposure to hepatitis A has been reported to shift from childhood to adolescent or adult age groups [5]. The statistical works carried out by the Ministry of Health between 1990 and 2005 show that the incidence of hepatitis A infections has decreased from 5325/100 000 to 1281/100 000 and the rate of mortality has decreased from 0.78/1 000 000 to 0.03/1 000 000 [8].

In a recent multicentered study carried out in our country, but that did not include the province of Konya, 4793 patients with chronic hepatitis B were investigated and the rate of anti-HAV IgG positivity was found to be 93.5% [9]. This rate is very close to the rate of anti-HAV IgG positivity that we found in chronic hepatitis B patients, which was 93.6%.

The anti-HAV IgG seropositivity in patients with a CLD has been reported in largely varying rates in the studies carried out in various countries of the world. In three different studies carried out in Italy on patients with a CLD, anti-HAV IgG seropositivity has been reported to be 79.3% [10] and 85.7% [11], and 97.64% in patients with chronic hepatitis C only [12]. In another multicenter study carried out in Italy, the rate of anti-HAV IgG seropositivity was 53.5% in 2830 patients with a CLD, the rate being higher in the south and middle provinces of the country and lower in the north [13]. The anti-HAV IgG seropositivity was 55% in patients with a CLD in the USA, another developed country [14].

In a study carried out in Saudi Arabia, anti-HAV IgG positivity was found to be as high as 98.5% in a group of 136 CLD patients whose mean age was 39.1 ± 17.6 years and it was concluded at the end of the study that the hepatitis A vaccine was not necessary for adult patients with CLD [15].

In another study carried out in the Kerala region of India, anti-HAV IgG positivity was found to be 93.3% in 300 CLD patients whose mean age was 53 ± 4 years, and at the end of the study it was suggested that routine vaccination should not be attempted before anti-HAV IgG was tested [16].

Anti-HAV IgG positivity was found to be 98.1% in adult patients with liver cirrhosis in Brazil and no routine vaccination was recommended at the end of the study [17].

In a study carried out in Iran, the anti-HAV IgG positivity was 79.2% in patients with chronic viral hepatitis, and hepatitis A vaccination was recommended for patients with chronic viral hepatitis who were younger than 30 years old [18].

A large number of studies have been carried out in Korea on this subject [19–24]. In one of the two recent studies, the anti-HAV IgG positivity was found to be 86.61% in patients with chronic viral hepatitis [19] and the anti-HAV IgG positivity was found to be 49.1% in the other study where only patients with chronic hepatitis B were assessed [20].

At the end of the study, being older than 40 years and living in a rural area were found to be independent risk factors for anti-HAV IgG seropositivity. The anti-HAV IgG positivity was found to be statistically higher in our study in patients older than 40 years compared with those younger than 40 years of age. Although an age above 40 years was found to be a risk factor for anti-HAV IgG seropositivity in the Korean study [19], the anti-HAV IgG seropositivity was found to be significantly higher in chronic hepatitis patients older than 30 years of age in a study carried out in Iran [18]. A study carried out by Saab *et al.* [14] in the USA has shown that patients aged between 51 and 70 years have a higher risk of being exposed to HAV than patients younger than 51 years of age. Studies have shown that the ages at which individuals

become infected have been shifting from young to old in developing countries [25,26].

When anti-HAV IgG positivity was assessed in terms of sex, no difference was found in most of the studies as in our study [13,14,20,21], but there are also study results showing that female sex is an independent risk factor [18,19]. More anti-HAV IgG seropositivity was found in female patients in the study carried out in Korea. They explained this finding by the fact that female patients in Korea have a larger number of social and household contacts and thus probably more exposure to HAV [19].

With respect to place of residence, we found in our study that living in a rural area was an independent risk factor for anti-HAV IgG seropositivity. Although in the study carried out in Korea the anti-HAV IgG seroprevalence was found to be the lowest in Seoul, the most developed city of Korea, the rate was found to be higher in rural areas as in our study [19]. In the study carried out in Italy, seroprevalence was found to be higher in the South of Italy than in the North and this was linked to improving hygiene and socioeconomic conditions in Northern Italy [13]. Such variances in seroprevalence may be associated with differences in living conditions.

No correlation was found in the present study between anti-HAV IgG seropositivity and hepatitis B/hepatitis C. This result is in agreement with those of other studies [14, 18,19]. This finding may indicate that the immune response to HAV infection is not affected by either hepatitis B virus or HCV.

There was also no difference between cirrhotic and noncirrhotic patients with respect to anti-HAV IgG seropositivity. However, the results of some studies indicate that the anti-HAV IgG seropositivity is higher in patients with liver cirrhosis than in those with chronic viral hepatitis [18,19]. They point out that the higher seropositivity of anti-HAV in older individuals may be explained by the fact that they lacked good hygiene practices in the past and were probably exposed to HAV, leading to the production of anti-HAV [18]. The result that we found may be linked to the fact that the number of cirrhotic patients was smaller than the number of patients with chronic hepatitis in our study.

Two doses (at months 0 and 6) of the hepatitis A vaccine were administered to 21 of the 31 patients who had been found to be anti-HAV IgG negative. Only eight of these 21 patients could be examined for the outcome and anti-HAV IgG was found to be positive in all of them. In a study, the IgG seroconversion was found to be 86.17% in patients with chronic hepatitis B after their hepatitis A vaccination [27]. However, no interpretation was attempted in this study on this issue because we could not vaccinate all the chronic viral hepatitis patients who were anti-HAV IgG negative and not all the patients that we could vaccinate attended follow-up.

Hepatitis A vaccines, which had initially been licensed to be used after age 2 as maternal antibodies showed persistence, were licensed by the Food and Drug Administration (FDA) after 2005 to be administered to children older than a year. Hepatitis A vaccine is recommended in the USA today for all children older than 1 year [28]. In 2012, the Ministry of Health in Turkey included the hepatitis A vaccine in the routine vaccination program to be administered at the end of month 18 as the first dose

and at the end of month 24 as the second in infancy [6]. This routine vaccination program is good news for the coming years for our country, which is in moderate endemicity for particularly chronic hepatitis B.

In conclusion, patients with CLD who are younger than 40 and/or living in cities may be at risk for hepatitis A infection. Such patients should be advised to seek hepatitis A vaccination following an anti-HAV IgG test.

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Conflicts of interest

There are no conflicts of interest.

References

- 1 Wasley A, Feinstone SM, Bell BP. Hepatitis A virus. In: Mandell GL, Bennet JE, Dolin R, editors. *Principles and practice of infectious diseases*, 7th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2010. pp. 2367–2385.
- 2 Mathiesen LR. The hepatitis A virus infection. *Liver* 1981; 1:81–109.
- 3 Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients chronic hepatitis C. *N Engl J Med* 1998; 338:286–290.
- 4 Franco E, Meleleo C, Serino L, Sorbara D, Zaratti L. Hepatitis A: epidemiology and prevention in developing countries. *World J Hepatol* 2012; 4:68–73.
- 5 Türker K, Balci E, Batı S, Hascuhadar M, Savaş E. The changing epidemiology of hepatitis A infection in Turkey [in Turkish]. *Türk Mikrobiyol Cem Derg* 2011; 41:143–148.
- 6 Tosun S. The changing viral hepatitis epidemiology in our country. *Ankem Derg* 2013; 27:128–134.
- 7 Melnick JL. History and epidemiology of hepatitis A virus. *J Infect Dis* 1995; 171 (Suppl 1):S2–S8.
- 8 Turkish Republic, The Ministry of Health. Hepatitis A number of cases and deaths, morbidity and mortality rates. 1990–2005, 2010. Available at: <http://www.saglik.gov.tr>. [Accessed 31 December 2010].
- 9 Celen MK, Turker K, Oztoprak N, Sener A, Tuna N, Ince N, et al. The evaluation of exposure to hepatitis A virus in HBsAg-positive persons: a multicenter study from Turkey. *J Pure Appl Microbiol* 2014; 8:3063–3068.
- 10 Sagnelli E, Rossi G, Coppola N, Scolastico C, Onofrio M, Filippini P, et al. Antibodies to hepatitis A virus in Italian patients with chronic liver disease. *Epidemiol Infect* 2001; 127:341–346.
- 11 Stroffolini T, Almasio PL, Di Stefano R, Andreone P, Di Gaetano G, Fattovich G, et al. Anti-hepatitis A virus seroprevalence and seroconversion in a cohort of patients with chronic viral hepatitis. *Dig Liver Dis* 2002; 34:656–659.
- 12 Bertino G, Ardiri AM, Bruno MC, Valenti M, Lerna D, Boemi PM, et al. HAV infection in patients with chronic hepatitis C. *Clin Ter* 2007; 158:223–225.
- 13 Sagnelli E, Stroffolini T, Almasio P, Mele A, Coppola N, Ferrigno L, et al. Exposure to HAV infection in patients with chronic liver disease in Italy, a multicentre study. *J Viral Hepat* 2006; 13:67–71.
- 14 Saab S, Lee C, Shpaner A, Ibrahim AB. Seroepidemiology of hepatitis A in patients with chronic liver disease. *J Viral Hepat* 2005; 12:101–105.
- 15 Singal AK. Hepatitis A vaccine is not required in adult patients with chronic liver disease in Saudi Arabia. *Singapore Med J* 2009; 50:442–443.
- 16 John A, Chatni S, Narayanan VA, Balakrishnan V, Nair P. Seroprevalence of hepatitis A virus in patients with chronic liver disease from Kerala: impact on vaccination policy. *J Indian Med Assoc* 2009; 107:859–861.
- 17 Oliveira LC, Comácio SM, Santos Jde F. Seroprevalence of hepatitis A immunity among Brazilian adult patients with liver cirrhosis: is HAV vaccination necessary? *Braz J Infect Dis* 2011; 15:268–271.
- 18 Ahmadi Vasmehjani A, Javeshghani D, Baharlou R, Shayestehpour M, Mousavinasab SD, Joharinia N, Enderami SE. Hepatitis A infection in patients with chronic viral liver disease: a cross-sectional study in Jahrom, Iran. *Epidemiol Infect* 2015; 143:534–539.
- 19 Cho HC, Paik SW, Kim YJ, Choi MS, Lee JH, Koh KC, et al. Seroprevalence of anti-HAV among patients with chronic viral liver disease. *World J Gastroenterol* 2011; 17:236–241.

- 20 Lee SH, Kim HS, Park KO, Park JW, Chun SY, Lim SJ, *et al.* Prevalence of IgG anti-HAV in patients with chronic hepatitis B and in the general healthy population in Korea. *Korean J Hepatol* 2010; 16: 362–368.
- 21 Kim do Y, Ahn SH, Lee HW, Kim SU, Kim JK, Paik YH, *et al.* Anti-hepatitis A virus seroprevalence among patients with chronic viral liver disease in Korea. *Eur J Gastroenterol Hepatol* 2007; 19:923–926.
- 22 Song HJ, Kim TH, Song JH, Oh HJ, Ryu KH, Yeom HJ, *et al.* Emerging need for vaccination against hepatitis A virus in patients with chronic liver disease in Korea. *J Korean Med Sci* 2007; 22: 218–222.
- 23 Kang JH, Lee KY, Kim CH, Sim D. Changing hepatitis A epidemiology and the need for vaccination in Korea. *Asian Pac J Allergy Immunol* 2004; 22:237–242.
- 24 Lee TH, Kim SM, Lee GS, Im EH, Huh KC, Choi YW, Kang YW. Clinical features of acute hepatitis A in the Western part of Daejeon and Chungnam province: single center experience. *Korean J Gastroenterol* 2006; 47:136–143.
- 25 Saberifiroozi M. Hepatitis A virus infection: is it an important hazard to public health? Hazards of HAV for public health. *Hepat Mon* 2011; 11:235–237.
- 26 Movahedi M, Haghdoost AA, Pournik O, Hajarizadeh B, Fallah MS. Temporal variations of health indicators in Iran comparing with other Eastern Mediterranean Region countries in the last two decades. *J Public Health (Oxf)* 2008; 30:499–504.
- 27 Cho HC, Kim YJ, Choi MS, Lee JH, Koh KC, Yoo BC, Paik SW. The seroconversion rate of hepatitis a virus vaccination among patients with hepatitis B virus-related chronic liver disease in Korea. *Gut Liver* 2011; 5:217–220.
- 28 Centers for Disease Control and Prevention. Birth-18 years & ‘catch-up’ immunization schedules; United States, 2015. Available at: <http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html>. [Accessed 26 June 2015].