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The Change in the Susceptible Populations with the Shift in Hepatitis A Epidemiology

Hepatit A Epidemiyolojisi ve Duyarlı Nüfusta Değişim

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ABSTRACT

Aim: The incidence of hepatitis A (HepA) has decreased due to vaccination and improved hygiene conditions. However, the age of onset of the disease has shifted from childhood to adulthood. Children with HepA are mildly symptomatic, whereas the course of the disease in adults may be severe. The aim of this study was to examine the change in HepA seroprevalence and identify the population susceptible to HepA.

Material and Methods: A total of 10132 patients who were tested anti-Hepatitis A virus immunoglobulin G (anti-HAV IgG) between 2016 and 2019 were reviewed retrospectively, and included in this study. The patients were divided into five groups according to their age, and seropositivity rates were compared between age groups. The relevant data of the healthcare professionals were also evaluated separately.

Results: The overall seropositivity rate was 60.1% (n=6088). The seropositivity rate was found 29.0% (n=944) in the 18 to 24 years range, 49.7% (n=837) in the 25 to 29 years range, 60.6% (n=689) in the 30 to 34 years range, 76.6% (n=784) in the 35 to 39 years range, and 93.3% (n=2834) in the ≥40 years groups. The seropositivity rate was found 36.1% (n=1781) and 82.9% (n=4307) in patients <30 and ≥30 years groups, respectively (p<0.001).

Conclusion: In recent decades, there has been a significant change in HepA seroprevalence. This change has resulted in the emergence of a young adult population susceptible to possible HepA outbreaks. Thus, seronegative young adults may be considered at risk for HepA and routine vaccination may be considered.

Keywords: Hepatitis A; hepatitis A virus; hepatitis A vaccine.

ÖZ

Amaç: Aşılama ve hijyen koşullarının iyileşmesi sayesinde hepatit A (HepA) insidansı azalmıştır. Bununla birlikte, hastalığın başlangıç yaşı çocukluk çağından yetişkinlik çağına doğru kaymıştır. HepA olan çocuklar hafif semptomatik iken erişkinlerde ise hastalığın seyri şiddetli olabilir. Bu çalışmanın amacı, HepA seroprevalansındaki değişimi incelemek ve HepA'ya duyarlı olan popülasyonu belirlemektir.

Gereç ve Yöntemler: Bu çalışmada, 2016 ve 2019 yılları arasında anti-Hepatit A virüsü immünoglobulin G (anti-HAV IgG) testi çalışılmış olan toplam 10132 hastanın verileri geriye dönük olarak incelendi ve çalışmaya dahil edildi. Hastalar yaşlarına göre beş gruba ayrıldı ve bu yaş grupları arasında seropozitiflik oranları karşılaştırıldı. Sağlık çalışanlarının ilgili verileri de ayrıca değerlendirildi.

Bulgular: Genel seropozitiflik oranı %60,1 (n=6088) idi. Seropozitiflik oranı 18 ile 24 yaş aralığında %29,0 (n=944) olarak, 25 ile 29 yaş aralığında %49,6 (n=837) olarak, 30 ile 34 yaş aralığında %60,6 (n=689) olarak, 35 ile 39 yaş aralığında %76,6 (n=784) olarak ve ≥40 yaş grubunda %93,3 (n=2834) olarak bulundu. Seropozitiflik oranı, <30 ve ≥30 yaş gruplarında, sırasıyla, %36,1 (n=1781) ve %82,9 (n=4307) olarak bulundu (p<0,001).

Sonuç: Son yıllarda, HepA seroprevalansında önemli bir değişiklik olmuştur. Bu değişiklik, olası HepA salgınlarına duyarlı olan genç bir yetişkin popülasyonun ortaya çıkmasına neden olmuştur. Bu nedenle seronegatif genç yetişkinler HepA açısından risk altında kabul edilebilir ve rutin aşılama yapılması düşünülebilir.

Anahtar kelimeler: Hepatit A; hepatit A virüsü; hepatit A aşısı.

INTRODUCTION

Approximately 1.5 million people worldwide are infected with the hepatitis A virus (HAV) annually. However, the actual number is estimated to be ten times higher (1). HAV is transmitted through the consumption of contaminated water and food and contact with infected persons (2).

Hepatitis A (HepA), defined as liver parenchyma infection caused by HAV is the most common form of acute viral hepatitis. Children with HepA are mildly symptomatic, whereas adults with HepA may have a serious clinical course, which may require hospitalization. Acute hepatitis usually resolves within two months. However, in approximately 10% of the patients, it may persist for up to 6 months or relapse. Rarely, it may also result in fulminant hepatitis and death (3).

HepA is a preventable disease by vaccination. Including the HAV vaccine in the national vaccination programs (NVP) and vaccinating people who have risk factors is recommended for countries in highly and moderately endemic regions (4). In accordance with these recommendations, the Ministry of Health of the Republic of Turkey included the HAV vaccine in its childhood NVP in 2012.

In addition to NVP, improved infrastructure and sanitary conditions caused a shift in the onset of HepA from childhood to adulthood (5). Therefore, it has been speculated that a group of adolescents and young adults who are not vaccinated may become susceptible to HAV, and thus, in a possible epidemic, loss of workforce, increased treatment costs, and increase in HepA-related morbidity and mortality may occur (6).

Most of the epidemiological studies on HepA in Turkey were conducted during the period when the HepA vaccine was not included in NVP (7-9). Only a few epidemiological studies examined the changes in the prevalence of HepA in adolescents and young adults who were not included in NVP. However, these studies may not fully reflect the changes in age-related HepA seroprevalence since they were conducted before the inclusion of the HAV vaccine in NVP (10-12).

This study aimed to examine the changes in HepA seroprevalence and to identify the population susceptible to HepA.

MATERIAL AND METHODS

This study was designed as retrospectively in İstanbul Medeniyet University Göztepe Training and Research Hospital. A total of 12814 patients who were tested for anti-Hepatitis A virus immunoglobulin G (anti-HAV IgG) between January 2016 and January 2019 were included. Patients under 18 years of age and repetitive test results were excluded. The remaining 10132 patients were included. Considering people under the age of 40 as young adults, we formed four groups under the age of 40 and one group over the age of 40. In this direction, the patients were divided into five groups according to their age; 18 to 24 years, 25 to 29 years, 30 to 34 years, 35 to 39 years, and over the age of 40. Based on previous studies, we divided the entire population into two groups as those under 30 years of age and above, since we considered those under 30 as the susceptible population (7-10). The serum samples were analyzed by the chemiluminescence microparticle immunoassay (Architect i2000, Abbott, U.S.) method. Per the manufacturer's instructions, anti-HAV IgG signal to cut-off (S/Co) values of less than 1 were considered negative, and greater than or equal to 1 were considered positive. The HAV-IgG seropositivity was compared between the groups.

The present study was performed in accordance with the principles of the Declaration of Helsinki, and the relevant national laws. The study protocol was approved by the Ethics Committee of İstanbul Medeniyet University with the decision number 2019/142).

Statistical Analysis

Descriptive statistics were reported as median, interquartile range, and minimum-maximum for numerical variables that were determined not to conform to the normal distribution, and as numbers and percentages for categorical variables. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to analyze the normality of numerical variables. The Mann-Whitney U test was used to compare two independent groups. In order to compare the categorical variables, Pearson's chi-squared test, and Fisher's exact test were used in 2x2 tables, and the Fisher-Freeman-Halton test was used in RxC tables. Jamovi project (Jamovi, version 2.2.5.0, 2022, retrieved from https://www.jamovi.org), Jeffreys' Amazing Statistics Program (JASP) software package (version 0.16.1, retrieved from https://jasp-stats.org), and R-project 4.1.3 for Windows (R Core Tea, R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, 2022, retrieved from https://www.R-project.org) software package were used in the statistical analysis. A p value of ≤ 0.05 was deemed to indicate statistical significance.

RESULTS

A total of 10132 patients who were tested for anti-HAV IgG between January 2016 and January 2019 were included. The patient characteristics were presented in Table 1. The overall anti-HAV IgG seropositivity rate was 60.1% (n=6088). The patients with anti-HAV IgG positivity were significantly older ($p<0.001$). In the subgroup analysis considering the age of the five groups, the groups also differed significantly in terms of the distribution of the anti-HAV IgG-positivity ($p<0.001$). The frequency of anti-HAV IgG-positivity increased from 29.0% to 93.3% as the age groups got older (Figure 1). The seropositivity rate was found as 29.0% (n=944) in the 18 to 24 years range group, 49.7% (n=837) in the 25 to 29 years range group, 60.6% (n=689) in the 30 to 34 years range group, 76.6% (n=784) in the 35 to 39 years range group, and 93.3% (n=2834) in the age of ≥40 years group. When the age was considered in two groups, <30 and ≥30 years old, the anti-HAV IgG-positivity rate was found as 82.9% (n=4307) in patients ≥30 years old, while it was 36.1% (n=1781) in patients <30 years old. A significantly higher prevalence of HAV infection was noted in patients ≥30 years old (OR=8.570, 95% CI: 7.812-9.402, $p<0.001$). There was a significantly higher number of male patients than female patients among the patients with anti-HAV IgG-positivity ($p<0.001$). While the rate of anti-HAV IgG-positivity was 66.6% (n=3108) in male patients, it was 54.5% (n=2980) in female patients. A significantly higher anti-HAV IgG-positivity was noted in male patients (OR=1.661, 95% CI=1.532-1.801, $p<0.001$). In

Table 1. Demographic and clinical characteristics of the patients

	Anti-HAV IgG Positivity (n=6088)	Anti-HAV IgG Negativity (n=4044)	p
Age (year), median (IQR), [min-max]	44 (35-54) [18-98]	22 (20-26) [18-77]	**<0.001**
Age groups, n (%)			
18-24 years	944 (29.0)	2306 (71.1)	
25-29 years	837 (49.7)	848 (50.3)	
30-34 years	689 (60.6)	448 (39.4)	**<0.001**
35-39 years	784 (76.6)	240 (23.4)	
≥40 years	2834 (93.3)	202 (6.7)	
Age group, n (%)			
<30 years	1781 (36.1)	3154 (63.9)	**<0.001**
≥30 years	4307 (82.9)	890 (17.1)	
Gender, n (%)			
Male	3108 (66.6)	1560 (33.4)	**<0.001**
Female	2980 (54.5)	2484 (45.5)	
Occupation, n (%)			
Healthcare Professionals	2302 (62.6)	1373 (37.4)	**<0.001**
Others	3786 (58.6)	2671 (41.4)	

Anti-HAV IgG: anti-Hepatitis A virus immunoglobulin G, IQR: interquartile range (25th-75th percentile)

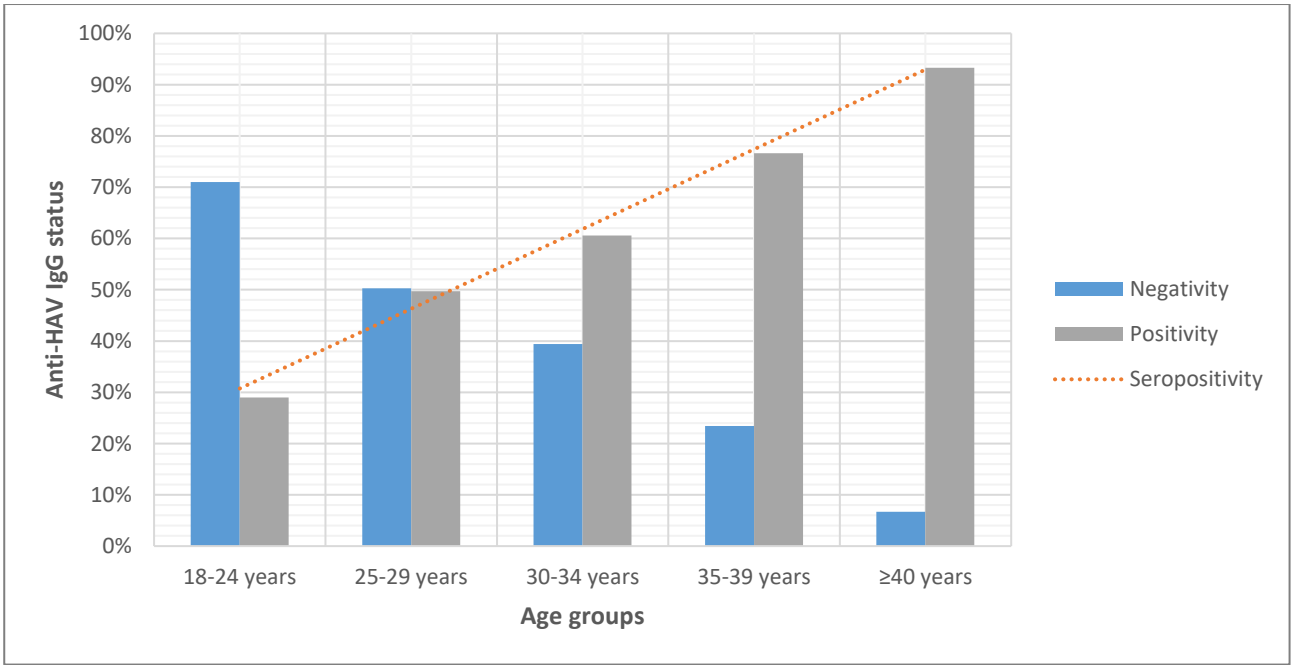

Figure 1. Distribution of patients' anti-HAV IgG characteristics by age groups

addition, there was a significantly higher number of healthcare professionals among patients with anti-HAV IgG-positivity (n=2302, 62.6% vs. n=3786, 58.6%, OR=1.183, 95% CI: 1.088-1.285, p<0.001).

The seropositivity rate among the healthcare professionals was 62.6% (n=2302/3675). The seropositivity rate of the healthcare professionals aged ≥30 years was 79.0% (1445/1829). The prevalence of HAV infection was also significantly higher among healthcare professionals aged ≥30 years (OR=4.343, 95% CI=3.756-5.020, p<0.001) than that among healthcare professionals aged <30 years (Table 2, Figure 2).

DISCUSSION

In the presented study, we investigated the anti-HAV IgG characteristics of a large cohort of patients in our tertiary care referral center which resides in the highly populated and cosmopolitan city of Istanbul. The anti-HAV IgG characteristics of the patients included in the study were analyzed to detect the HepA seroprevalence according to the age groups and determine the population susceptible to HepA. We demonstrated that the seropositivity in younger age groups was low and increased with age.

Globally, the incidence of HAV has decreased in the last two decades due to increased accessibility to clean water

Table 2. The distribution of anti-HAV IgG characteristics in healthcare professionals aged<30 and ≥30 years

	Anti-HAV IgG Positivity (n=2302)	Anti-HAV IgG Negativity (n=1373)	p
Age group, n (%)			
<30 years	857 (46.4)	989 (53.6)	**<0.001**
≥30 years	1445 (79.0)	384 (21.0)	

Anti-HAV IgG: anti-Hepatitis A virus immunoglobulin G

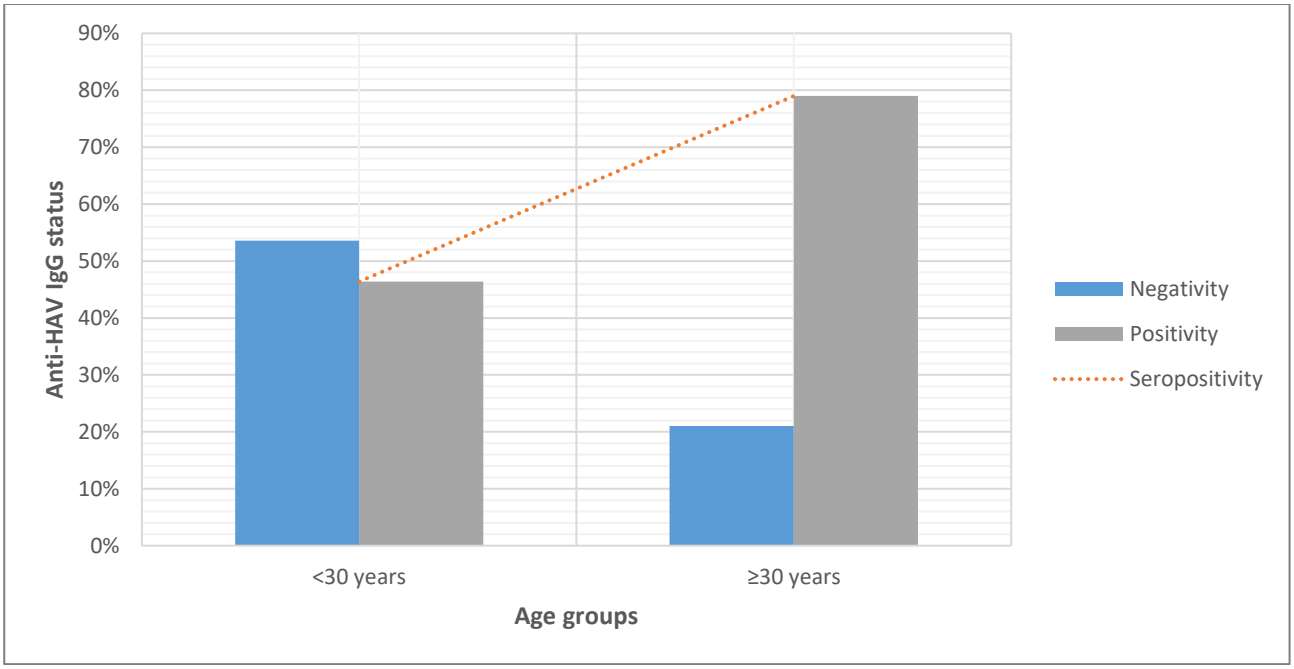

Figure 2. Distribution of healthcare professionals' anti-HAV IgG characteristics by age groups

resources and improved sanitary conditions (5). Similarly, the incidence of HepA tends to decrease in Turkey but still, the seropositivity rate in the general population was found to be between 74-91% (8-10). In comparison, the seropositivity rate was found as 60% in this study.

The frequency of HepA infection is closely related to the countries' development level and socioeconomic status. In this context, HepA seropositivity in young adults has gradually decreased in developed countries yet remains high in developing countries (13). HepA seropositivity rate in the 20-25-year-old age group was 13% in North America, 35% in Western Europe, 91% in South Asia, 83% in the Middle East and North Africa, and 100% in Sub-Saharan Africa (5).

In a study conducted in South Korea, seropositivity was found to be low in young adults (12.7%, 16.0%, and 26.7% in 20-24, 25-29, and 30-34-year-old age groups, respectively). On the other hand, it was observed that the incidence of acute HepA increased in individuals aged 20-39 years and that severe hepatitis clinic-related hospital admissions and treatment costs increased with age (14). The range of seropositivity rate in the below-30-year-old age group reported in the studies that investigated the seroprevalence by age in Turkey was 57.1-83.6% (8-10). In a prospective study with 630 individuals in Istanbul in 2012, the seropositivity rate in the 20-24-year-old age group was 69% (7). In comparison, the seropositivity rates of our cohort in the 18-24- and 25-29-year-old age groups were 29.0% and 49.7%, respectively. The seropositivity rate was found as 36.1% in the below-30-year-old age group in our study, indicating a significant difference between the below-30 and over-30-year-old age groups in that respect.

Given that there was a significantly lower number of patients with seropositivity among young adults can be attributed to the vaccination campaign intended for children, which plays an important role in contagiousness, and the improvement of sanitary conditions.

HepA incidence in the European Union Countries also decreased between 1997 and 2011, from 10.0 to 2.5 per 100,000 population. However, outbreaks have been reported in recent years due to travel to highly endemic areas, frozen imported foods, and risky sexual behavior (15). In 2017, 649 HepA cases were reported in the California State of U.S. as part of the epidemic originating from homeless people. Of these cases, 417 people were hospitalized, and 21 died (16). These data indicate that even in developed countries, the vaccination rate of people with risk factors remains low, and the disease may be disregarded.

The healthcare workers are considered to be in the risk group for HAV infection. In the study by Kutlu et al. (17) conducted with students in the faculty of dentistry, HAV IgG-positivity was found to be 24.9%, and the majority of the students were found to be susceptible to HepA. In comparison, the seropositivity rate in healthcare professionals in the below-30-year-old age group in this study was 46.4%. The difference between the seropositivity rates in our study may be attributed to the fact that the students are typically aged below 25. The serology of healthcare professionals in the high-risk group should be analyzed, and adequate efforts should be made, especially for the immunization of young healthcare professionals.

HepA vaccine is very effective and safe in preventing the disease. Healthcare professionals, sewer workers, travelers to countries located in highly endemic regions, chronic liver disease patients, and men who have sex with men are considered risky groups for HepA and are recommended to have the HepA vaccine (18,19). Other than these risk groups, the HepA vaccine was not found to be cost-effective in studies conducted for routine vaccination of adults with the HepA vaccine. However, these studies were carried out only in countries located in slightly endemic regions and did not cover the countries located in moderately endemic regions such as Turkey (20,21) and it

is a shortcoming that the riskier seronegative adults living in countries located in the moderately and highly endemic regions are not recommended to have the vaccine. Additionally, the refugee influx from the Middle East, which is a highly endemic region, to moderately to slightly endemic countries, including Turkey, increases the risk for HepA outbreaks even more.

Including young adults in the national vaccination programs will raise concerns about the increase in health expenditures. However, it may be possible to reduce the cost of vaccination by maintaining the effectiveness of immunization. As a matter of fact, Curran et al. (22) demonstrated the efficacy and safety of a single dose of the HAV vaccine using a mathematical modeling method in the Mexican Public Health System. In studies, the effectiveness of the vaccine was found to be >98% in the first 10 years with a single dose vaccination. However, it was observed that antibody titers decreased in the following years. Double-dose vaccination is preferred because there is insufficient data on single-dose vaccination. There is a need for studies evaluating the cost-effectiveness of a single dose of the HepA vaccine (23,24).

CONCLUSION

Including young adults susceptible to HepA in the groups recommended for being vaccinated with the HAV vaccine may be considered. Further studies on single-dose HAV vaccination are needed in the context of reducing the cost of vaccination. Additionally, prospective studies are needed to evaluate the epidemiology and prognosis of acute HepA in adults and the cost-effectiveness of vaccinating seronegative young adults.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of İstanbul Medeniyet University (27.03.2019, 142).

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The authors were working in the institution where the study was conducted at the time of the study.

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