

Hepatitis A seroprevalence and demographic risk factors in the susceptible population: a cross-sectional study

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Abstract. – OBJECTIVE: The epidemiology of hepatitis A virus (HAV) infection is influenced by variables such as age, sex, environmental conditions, and vaccination status. This study aimed to evaluate HAV seropositivity after the inclusion of hepatitis A vaccination in the national childhood immunization program and identify demographic risk factors of the susceptible population before routine vaccination.

PATIENTS AND METHODS: This cross-sectional epidemiological study was conducted by retrospectively examining the laboratory records of patients who underwent HAV serology testing in a tertiary care center in eastern Turkey between 2008 and 2019.

RESULTS: Overall immunity to HAV was 81.6%. According to birthplace and year, the rate of anti-HAV positivity was higher among people born before 2006 in the Southeast and Eastern Anatolia regions. For those born in 2012 or later, the lowest seropositivity was among those born in the Southeast region, while it was over 60% in the other regions. When analyzed by year of birth, the lowest seropositivity was in those born between 1994 and 2011, and the frequency of seropositivity increased with age. Of those born between 1982 and 1999, the seropositivity rate was higher among men than women. Rural dwellers born before 2012 had higher seropositivity than urban dwellers. Among those born before the introduction of routine childhood HAV vaccination, female sex, urban dwelling, and each additional year of age were identified as independent demographic risk factors for HAV susceptibility.

CONCLUSIONS: Socioeconomic development and immunization programs have altered HAV seroprevalence patterns. Planning catch-up vaccinations, especially in adolescents and young adults (born in 1994-2011) with low seropositivity and ensuring the continuity of hygiene and sanitation practices are important to protect the susceptible population.

Key Words:

Hepatitis A, Immunization, Seroepidemiology, Turkey.

Introduction

Hepatitis A virus (HAV) is a viral hepatitis agent that causes symptoms of varying severity, ranging from asymptomatic infection to fulminant hepatitis^{1,2}. Unlike hepatitis B and C, hepatitis A usually presents as acute hepatitis^{1,3}. Every year, 1.5 million new HAV infections are reported worldwide⁴. HAV infection caused 7,134 deaths worldwide in 2016, accounting for 0.5% of all viral hepatitis mortality². HAV is transmitted through the fecal-oral route, which includes direct contact with infected individuals and consumption of contaminated food or water^{1,2}. Therefore, hygiene practices, socioeconomic conditions, and access to clean water sources are the main reasons for differences in geographical distribution. Vaccination against HAV also affects its epidemiology².

Turkey is regarded as a moderately endemic area for HAV, and the prevalence of anti-HAV immunoglobulin G (IgG) was reported as 64.4% in a study conducted in five different geographical regions of Turkey^{3,5}. The prevalence may also vary among different study regions and residential areas³. The incidence of hepatitis A in Turkey has declined since 2007, falling to less than 5/100,000 after 2015⁶. At the same time, the age at exposure to HAV has shifted toward adolescence and young adulthood⁷. This can be explained by improvements in hygiene conditions and water sanitation in recent years^{3,8}. Although the inactivated HAV vaccine has been used safely

and effectively elsewhere in the world since 1992, it was only included in the routine childhood vaccination program of Turkey in 2012^{7,9}. As new HAV infections can be much more persistent and aggressive in adults, HAV vaccination is especially recommended for this age group in areas of infection risk⁸.

Anti-HAV IgG antibody levels and the age-specific prevalence of HAV infection among people born in different years are important indicators for predicting the risk of acquiring HAV infection¹⁰. The aim of this study was to evaluate the prevalence of HAV seropositivity after the inclusion of the HAV vaccine in the national vaccination program and to determine demographic risk factors for susceptibility in the pre-vaccination population.

Patients and Methods

This cross-sectional epidemiological study was conducted in a regional tertiary care hospital in the Eastern Anatolia region of Turkey. As a regional hospital, our center receives referrals from neighboring provinces. In addition, as people from various occupational groups are appointed to our city within the service obligation scheme, our center also serves individuals born in different regions of Turkey.

This study included 25,884 patients who were evaluated for anti-HAV IgG antibodies between 2008 and 2019. The distribution of patients in-

cluded in the study according to place of birth is shown in Figure 1. Most (83.0%) of the patients were born in the Eastern Anatolia region. The patients were being followed up for various medical diagnoses, and the most common reason for presentation (30.4%) was general medical observation and examination. For patients with multiple entries, the earliest chronological result was used in the analysis and the others were excluded. To enable the best comparison with the available literature data, age groups were selected according to birth dates, also taking into account the start of national HAV vaccination in 2012. As a result, birth dates were grouped by year as those in 2012 and later (A), 2006-2011 (B), 2000-2005 (C), 1994-1999 (D), 1988-1993 (E), 1982-1987 (F), and 1981 and earlier (G). Patients under the age of 1 were excluded because of the presence of maternal antibodies. Based on the patient's age at the time of HAV serology, we also calculated the median age and age range for each group in order to compare our results with those of studies evaluating by age group. These values were as follows: A=4 (1-8), B=7 (4-13), C=12 (6-19), D=17 (10-25), E=24 (16-32), F=30 (23-38), and G=53 (29-100).

Anti-HAV IgG antibody quantification was performed by enzyme-linked immunosorbent assay in the hospital microbiology laboratory. Cut-off values were determined according to the manufacturer's instructions for the assay kits. The results were recorded retrospectively in the hospital information system.

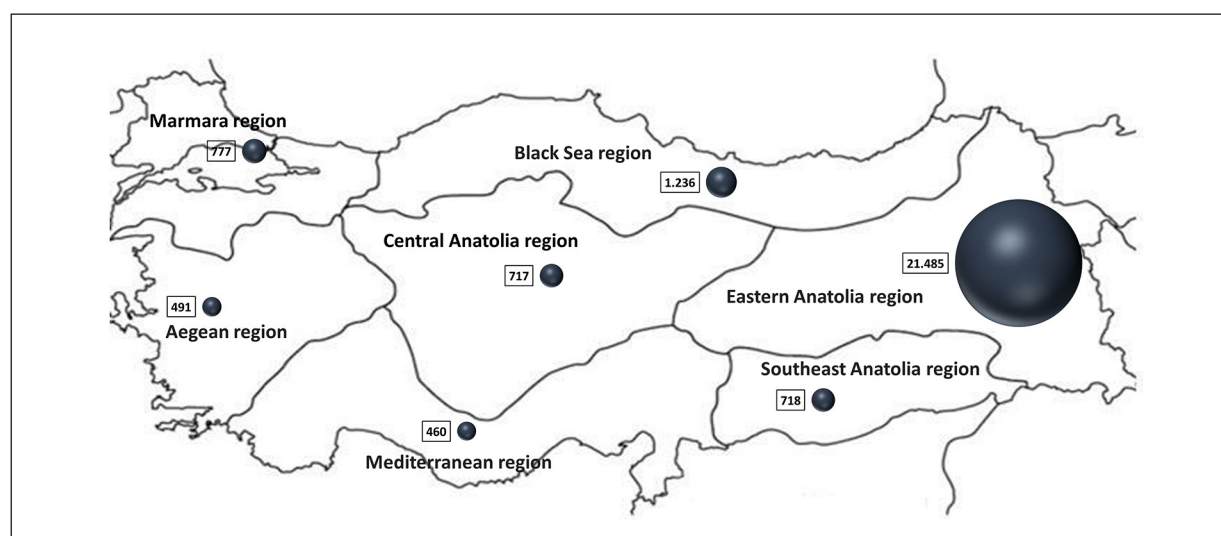


Figure 1. Distribution of patients by place of birth.

Statistical Analysis

The data were analyzed using the SPSS version 21.0 statistical software package (IBM Corp., Armonk, NY, USA). For descriptive statistics, categorical data were presented as frequency distribution and percentage. Categorical variables were compared between groups using the Chi-squared (χ^2) test. Multiple regression analysis was performed to determine the demographic risk factors associated with hepatitis A susceptibility (model: backward: LR. entry: 0.05 and removal: 0.10). Results with a p -value <0.05 were considered statistically significant.

Results

The patients included in this study had a median age of 32.0 (range, 1-100) and 54.5% were male. The overall rate of anti-HAV IgG positivity was 81.6% ($n=21,124$). Differences in HAV seropositivity according to birthplace and year are shown in Figure 2. HAV seropositivity among people born in 2012 or later was lowest (43.8%) in those born in the Southeast Anatolia region and it was over 60% in other regions. In all regions except Southeast Anatolia, seropositivity was lowest among people born between 2000 and 2011. People born before 2006 in the Southeast and Eastern

Anatolia regions had higher seropositivity than those in other regions. The rate of anti-HAV positivity increased with age in all regions and was over 85% among people born in 1981 or earlier. Anti-HAV IgG positivity status of the patients by date of birth, sex, and region are shown in Table I. Total Anti-HAV IgG positivity differed significantly in all pairwise comparisons between age groups ($p<0.001$) except between those born in or after 2012 and those born in 1988-1993 ($p=0.204$). The lowest rate of anti-HAV IgG positivity was in people born in 2006-2011 (43.5%) and the highest was in those born before 1981 (97.8%) ($p<0.001$). Anti-HAV IgG positivity was significantly higher in males (82.8%; $n=11,679$) than in females (80.2%; $n=9,445$) ($p<0.001$). This difference was due to the higher rate of anti-HAV IgG positivity in males born between 1982 and 1999 ($p<0.001$). Anti-HAV IgG positivity was significantly higher among rural dwellers (89.2%; $n=12,435$) than urban dwellers (72.8%; $n=8,689$) ($p<0.001$). This difference was associated with the higher HAV seropositivity in rural dwellers born between 1982 and 2005 ($p<0.001$). In those born in or after 2012, the rate of anti-HAV IgG positivity among city dwellers slightly exceeded that of rural dwellers ($p=0.910$). The results of multivariate logistic regression analysis to determine independent risk factors for hepatitis A sus-

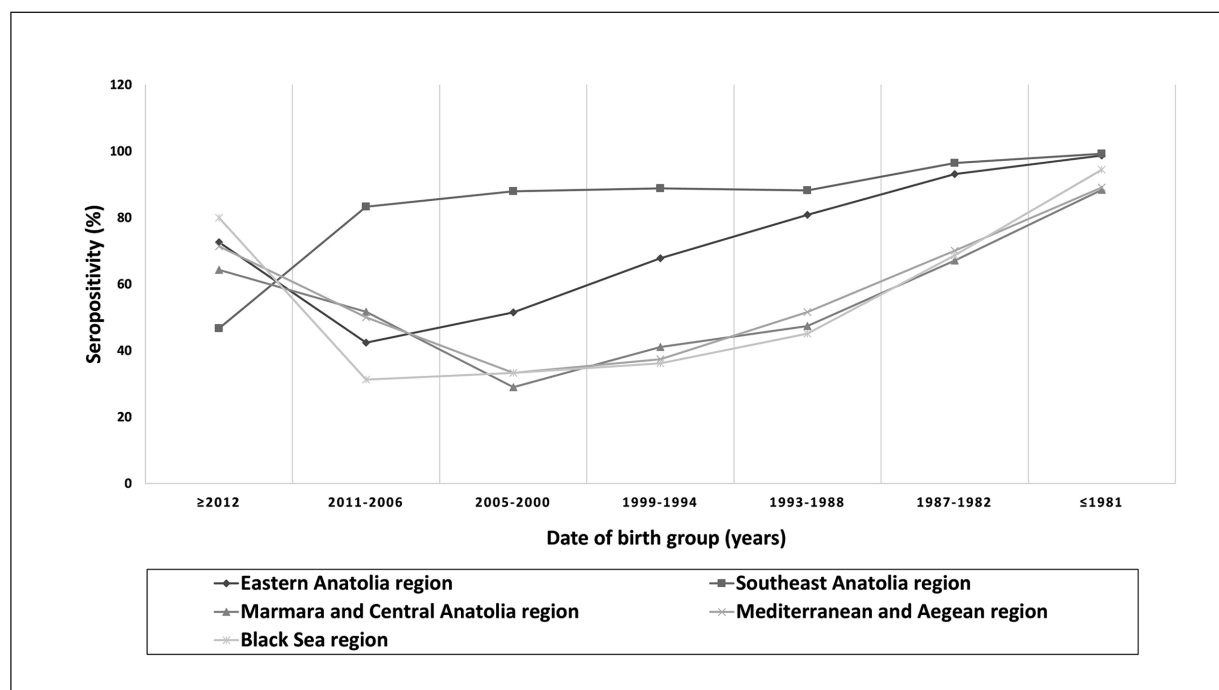


Figure 2. Rates of HAV seropositivity according to place and date of birth.

Table I. Anti-HAV IgG positivity status according to year and place of birth.

Year of birth	Male n (%)	Female n (%)	<i>p</i> *	Rural n (%)	Urban n (%)	<i>p</i> **	Total n (%)
≥ 2012 ^A	208 (70.5)	146 (73.7)	0.435	95 (71.4)	259 (71.9)	0.910	354 (71.8)
2006-2011 ^B	274 (44.5)	176 (42.0)	0.430	145 (47.4)	305 (41.8)	0.100	450 (43.5)
2000-2005 ^C	778 (50.5)	571 (49.8)	0.705	690 (65.6)	659 (40.3)	< 0.001	1.349 (50.2)
1994-1999 ^D	1.302 (68.3)	971 (60.2)	< 0.001	1.158 (74.6)	1.115 (56.7)	< 0.001	2.273 (64.6)
1988-1993 ^E	1.253 (77.8)	1.154 (71.2)	< 0.001	1.262 (80.9)	1.145 (68.5)	< 0.001	2.407 (74.5)
1982-1987 ^F	1.300 (89.8)	1.079 (83.3)	< 0.001	1.284 (90.6)	1.095 (82.6)	< 0.001	2.379 (86.7)
≤ 1981 ^G	6.564 (98.0)	5.348 (97.6)	0.076	7.801 (98.4)	4.111 (96.7)	0.479	11.912 (97.8)
							<i>p</i> *** < 0.001 †G > F > E, A > D > C > B

*p** = difference between the sexes. *p*** = difference between areas of residence. *p**** = difference between age groups. †*p* = 0.204 between groups E and A, *p* < 0.001 between other groups.

ceptibility after excluding people born after the HAV vaccine was included in the national routine immunization program (≥2012) are presented in Table II. The risk of hepatitis A susceptibility independently increased by 1.1-fold with each additional year of age, 2-fold in city-dwellers, and 1.3-fold in females.

Discussion

Hepatitis A seroprevalence varies in different geographical regions according to socioeconomic status, hygiene conditions, and age groups^{5,11}. The incidence of HAV infection has been shown to be inversely associated with the Human Development Index and per capita gross domestic product, which are indicators of socioeconomic development¹¹. A study⁵ of HAV prevalence in the pre-vaccination period in different geographical regions of Turkey indicated higher rates of HAV seropositivity in the Eastern and Southeast Anatolia regions, which also rank lowest in socioeconomic development indicators^{12,13}. In our study, we analyzed regional distribution based on place of birth and obtained similar results. We interpreted the higher HAV seroprevalence observed

in all groups born before 2012 in the Eastern and Southeast regions as a result of conditions experienced in childhood.

In a multicenter study in 2008, seropositivity was detected in over 80% of the 5-9 age group in the Eastern Anatolia region, where the majority of our cases were included⁵. In our study, we determined a lower rate of seropositivity in this age group (46.5%). We attribute this difference to improvements in sanitation and hygiene over time. Our results are consistent with those of another recent Turkish study showing that anti-HAV seroprevalence was lower in the 6-9 age range after excluding those born after vaccination. Increasing age was also associated with higher anti-HAV positivity, similar to our findings¹⁰. A systematic review of hepatitis A seroprevalence in Korea indicated that HAV seropositivity in the 21-30 age group decreased from 95% in 1989 to 18.8% in 2011¹⁴. These results show that efforts to close the hepatitis A immunity gap, especially in young adults, can strengthen overall protection from HAV, and our findings in this study demonstrate that catch-up vaccination against HAV is necessary for people born between 2000 and 2011.

In a study¹⁵ comparing the pre- and post-vaccination periods in the United States, a small

Table II. Independent risk factors for hepatitis A susceptibility.

	Odds ratio	95% confidence interval	<i>p</i>
Year of birth	1.103	1.099-1.107	< 0.001
City residence	2.062	1.911-2.225	< 0.001
Female sex	1.308	1.215-1.409	< 0.001

Log likelihood = 17,415.209, Cox & Snell R Square = 0.231200.

increase in anti-HAV antibody was observed in the post-vaccination period. This increase was attributed to the high anti-HAV positivity in children targeted by routine vaccination in the post-vaccination period. In our study, anti-HAV positivity was lower in those born after vaccination compared to the general seropositivity rate but was significantly higher than in those born immediately before vaccination (2011-1994). Although our study also offers no clear evidence of vaccine-induced immunity, this suggests that national hepatitis A vaccination plays a major role.

In general, the incidence of hepatitis A is higher in males than females¹⁶. Our study supports this historical data, as the rate of anti-HAV IgG positivity was higher among males in all age groups except those born after 2012. Studies^{17,18} evaluating sex-specific hepatitis A incidence trends in China and South Korea showed that the male-female disparity has narrowed over time since the hepatitis A vaccine was included in childhood routine vaccination programs. The reversal of the classical male-female difference in seroprevalence observed in our study in the group born after HAV vaccination began in 2012 may be a result of equal access to vaccination and vaccine-induced immunity.

We determined that hepatitis A seroprevalence was found to be higher among rural dwellers, consistent with the literature¹⁰. Also consistent with the literature, we observed no difference in hepatitis A seroprevalence between urban and rural dwellers in the 6-19 age group. This may be attributable to improved hygiene among young people and the vaccination program having equal inclusiveness in both urban and rural areas.

Within the scope of hepatitis A control programs, HAV vaccination is recommended for risk groups including patients with chronic liver disease, chronic HBV/HCV infection, HIV/AIDS, coagulation disorders, solid organ and bone marrow transplant candidates, gay/bisexual men, sewage workers, and healthcare professionals⁷. Apart from these risk groups, in this study we identified female sex, living in an urban area, and increasing age as demographic risk factors for susceptibility to hepatitis A. Consideration of these risk factors may allow more efficient targeting of hepatitis A vaccination efforts.

Limitations

The main limitation of this study is the retrospective data analysis. Secondly, although we included a large cohort from a large center, an

overview of Turkey is limited to the patients' places of birth. Therefore, a multicenter study including a more comprehensive nationwide sample is needed.

Conclusions

Measures to prevent fecal-oral transmission of HAV are needed in rural areas with low socioeconomic status. In addition to continuing the routine vaccination program, hepatitis A catch-up vaccination is recommended for adolescents and young adults (born between 1994 and 2011) with low seropositivity due to the possibility of greater disease severity in case of infection.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contribution

E.F. Karasahin and O. Karasahin designed the study, collected the data, and wrote the manuscript. E.F. Karasahin analyzed the data. All authors read and approved the final manuscript.

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Ethics Approval

The study received approval from the Clinical Research Ethics Committee of the Erzurum Regional Training and Research Hospital (Erzurum BEAH KAEK 2022/05-41 Date: 18.04.2022).

Informed Consent

Since the study was retrospective and did not include personal information, informed consent was waived.

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