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Shifting Seropositivity for Hepatitis A in Children in Istanbul, Turkey, From 1996 to 2011 and Evaluation of Hepatitis A-Associated Risk Factors

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Abstract

Hepatitis A virus (HAV) is transmitted by the fecal-oral route, and the epidemiology of HAV is associated with hygiene and socioeconomic status. In this study, we investigated the seropositivity for HAV and the associated socioeconomic factors in children. In addition, we compared the results with previously reported seropositivity data from the same center in Uskudar, Istanbul, Turkey, from 1996. A number of 400 children aged between 2-18 years, from the outpatient clinics, were tested for anti-HAV IgG antibodies and a questionnaire was administered that addressed gender, age, number of household members, monthly family income, history of jaundice and immunization, number of rooms in the house, education level of the parents, day-care/school attendance, and type of water supply. The overall seropositivity was 12.5%. The seropositivity increased with increasing age: 11.5% in children 2-<6 years old and 13.2% in children 10-18 years old. Significant associations between anti-HAV seropositivity and socioeconomic status, a history of jaundice, monthly family income were found ($p<0.001$, $p<0.001$, $p=0.04$, respectively). Also children under 6 years old, who were attending day-care had higher seropositivity rates. Only the association between the history of jaundice and anti-HAV seropositivity remained significant in the multivariate analysis, with an adjusted Odds ratio of 13.1 (95% CI, 2.9-59.5; $p=0.001$). There was a significant decline in the overall seropositivity for anti-HAV between 1996 and 2011. The frequency and severity of clinical HAV infection may increase in older age groups, and as a consequence, outbreaks can occur.

Keywords: anti-HAV; Hepatitis A; Hygiene; Seropositivity; Turkey.

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Introduction

Hepatitis A virus (HAV) is an enteric viral infectious disease that is endemic in Turkey [1, 2]. Asymptomatic or subclinical infection often occurs in children, and symptomatic acute infections are more common in adolescents and young adults. Asymptomatic or milder forms are underreported, and thus, the epidemiological pattern is determined primarily by seroprevalence. The number of HAV infections has decreased substantially in developed and developing countries in recent decades due to improvements in sanitation [1, 3- 5].

An epidemiological transition is occurring in many countries, and the proportion of susceptible adults is increasing [6]. Global hepatitis A risk maps show that Turkey transitioned from a very-high-risk category in 1990 to a low-risk category in 2005,

meaning that the age at which at least half of the population in that age group has anti-HAV IgG antibodies increased from <5 years to 5-14 years [7]. Because of the shifting epidemiological profiles of HAV, there is a need for up-to-date information from all over the world [7].

The aims of the present study were as follows: (1) to determine the current rate of anti-HAV seropositivity in relation to age in children referred to an outpatient clinic, (2) to evaluate infection-associated risk factors and (3) to compare the results with previously reported seropositivity data from the same center in Uskudar, Istanbul, Turkey, from 1996.

Materials and Methods

This hospital-based prospective study was conducted from November 2010 to March 2011 in the Zeynep Kamil Maternity and Children's Diseases Training and Research State Hospital in Istanbul, Turkey. Informed parental consent was obtained for all subjects, and the study was approved by the local ethics committee.

The inclusion criteria were age greater than two years old, no history of receiving the hepatitis A vaccine, referral to a pediatric outpatient clinic with symptoms other than jaundice and parental consent. Children with a known chronic disease or immune dysfunction were excluded from the study. To overcome the interference from maternal HAV antibodies, which are detected in 36.1% of infants aged 12 months and in 0.7% of infants aged 21 months, the lower limit for age was set to two years [2].

A questionnaire was administered that addressed gender, age, number of household members, monthly family income, history of jaundice and immunization, number of rooms in the house, education level of the parents, day-care/school attendance, and type of water supply. The information was obtained from the parents of the children. The Socio Economic Status (SES) score of each child was determined by summing the scores for monthly family income, education level of the parents, number of rooms in the house and number of people living in the house. The number of persons in the household was categorized as ≥5 or ≤4 persons (≥5 persons=1, ≤4 persons=2). The number of rooms in the house was categorized as ≥4 or ≤3 rooms (≤3 rooms=1, ≥4 rooms=2). Monthly family income was classified into 4 categories: very-low-income (<500 Turkish lira (YTL) (2.1 YTL ~1 U.S. dollars) per month), low-income (500-<1000 YTL), medium-income (1000-<2000 YTL) and high-income (≥2000 YTL) (very low=1, low=2, medium=3, high=4). The father's and mother's education levels were classified as illiterate=0, primary school=1, secondary school=2, high school=3 and university=4. The SES scores of the children ranged from 3 to 16, and the socioeconomic levels were grouped as follows: 3-5 low, 6-11 middle and 12-16 high.

Blood samples (3 mL) were collected and analyzed daily at the Microbiology Laboratory of the Zeynep Kamil Maternity and Children's' Diseases Training and Research Hospital. Anti-HAV IgG antibodies were detected using an enzyme-linked immunosorbent assay (LIAISON® Anti-HAV Assay, DiaSorin Inc., Saluggia, Italy) according to the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (version 17.0; SPSS Inc., Chicago, IL, USA). Univariate analysis was conducted using the χ^2 test to evaluate the relationships between sociodemographic parameters and anti-HAV seropositivity. A logistic regression model was used to assess the independence of these relationships. The Odds ratios and the 95% Confidence Intervals (CI) were calculated for the sociodemographic parameters. A p-value of <0.05 was considered statistically significant.

Results

The mean age of the 400 children was 7.9±3.7 years (range: 2-18). The male/female ratio was 195/205. A high monthly income was documented in 9.5% of the families. A high education level (university) was reported by 4.5% of the mothers and 5.5% of the fathers.

Of the 400 serum samples collected, all were tested for anti-HAV IgG, and 50 (12.5%) were positive. The rates of anti-HAV seropositivity within the age groups of 2-<6, 6-<10 and 10-18 years were determined. The seropositivity increased with

increasing age: 11.5% in the 2- to <6-year-old group and 13.2% in the 10- to 18-year-old group. The total anti-HAV positivities of the different age groups were not significantly different from each other (p=0.91). There was no significant difference in seropositivity between male and female participants (Table 1).

Table 1: Risk factors associated with anti-Hepatitis A virus seropositivity in the univariate analysis.

Social demographic features		Number (%)	Anti-HAV positivity		p-value
			n = 50	%	
Gender	Female	205 (51.3)	24	11.7	0.62
	Male	195 (48.8)	26	13.3	
Age groups	2-<6 years	122 (30.5)	14	11.5	0.9
	6-<10 years	149 (37.3)	19	12.8	
	10-18 years	129 (32.3)	17	13.2	
Socio-economic status	High	59 (14.7)	10	16.9	<0.001
	Middle	316 (79)	31	9.8	
	Low	25 (6.3)	9	36	
Day care/school attendance	Yes	232 (58)	35	15.1	0.06
	No	168 (42)	15	8.9	
	Age groups:				
	2-<6 years	122 (30.5)	14	11.5	0.003
	6-18 years	278 (69.5)	36	12.9	
Monthly family income	<500 YTL	27 (6.8)	6	22.2	0.04
	500-<1000 YTL	215 (53.8)	21	9.8	
	1000-<2000 YTL	120 (30)	14	11.7	
	≥2000 YTL	38 (9.5)	9	23.7	
Type of water supply	Tap water	83 (20.8)	13	15.7	0.41
	Spring water	245 (61.3)	32	13.1	
	Processed water	29 (7.3)	2	6.9	
	Other	43 (10.6)	3	7	

History of Jaundice	Yes No	8 (2) 392 (98)	5 45	62.5 11.5	<0.001

Significant associations between anti-HAV seropositivity and the SES, age under 6 years old and attending day-care, a history of jaundice, monthly family income and were found ($p<0.001$, $p=0.003$, $p<0.001$, $p=0.04$, respectively, χ^2 test). Only the association between the history of jaundice and anti-HAV seropositivity remained significant in the multivariate analysis, with an adjusted Odds ratio of 13.1 (95% CI, 2.9-59.5; $p=0.001$) (Table 2).

Table 2: Analysis of role of factors in detecting anti-HAV seropositivity.

	Odds Ratio	95% CI		p-value
		Lower	Upper	
Education level of the mothers	0.1	0.01	1.5	0.11
History of jaundice	13.1	2.9	59.5	0.001
Socioeconomic status	0.9	0.7	1.1	0.59

Sociodemographic factors such as the number of rooms, the number of members in the household, the education levels of parents and the type of water supply did not show any association with HAV seropositivity ($p>0.05$, univariate χ^2 test). The anti-HAV seropositivity data from the current study were compared with those from a previous study that was performed at the same center in Istanbul, Turkey, in 1996 [unpublished data, congress abstract: Hepatitis A virus and Hepatitis B virus seroprevalence of 0-15 age group. Zeynep Kamil Hospital, Istanbul. 20th International Congress of Chemotherapy. Sydney, Australia, June 29-July 3, 1997, pp2278]. The previous study included 830 non-vaccinated children aged between 2-18 years. Demographic parameters were not statistically different with the current study. There was a significant decline in the overall seropositivity for anti-HAV between 1996 and 2011 ($p<0.001$). In 1996, the overall seropositivity was 41.3%. In the 1996 study, the seropositivity was 35.2% in 2- to <6-year-old age group, 35.3% in the 6- to <10-year-old age group and 54.3% in children older than 10 years (Figure 1).

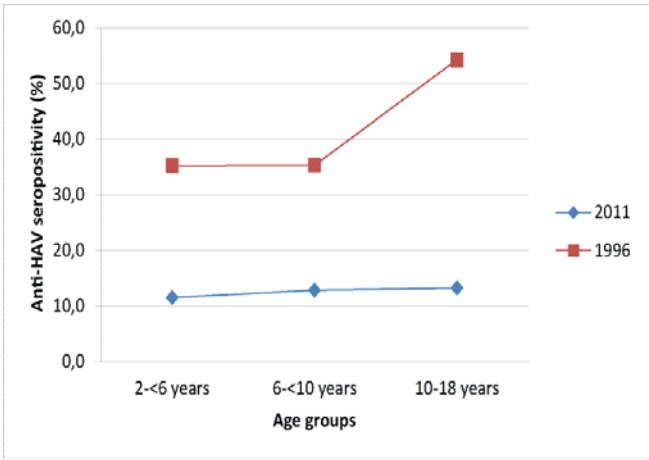

Figure 1: Shifting seropositivity for antibodies against hepatitis A virus in the age groups of 2-<6, 6-<10 and 10-18 years in Uskudar, Istanbul, Turkey, in 1996 and 2011.

Discussion

According to the rate of seropositivity (12.5%), the majority of children who were included in our study are susceptible to HAV infection. Over the years, the incidence of HAV infection has decreased with the improving hygienic and socioeconomic statuses and improving living conditions. Parallel with this decrease in incidence has been an increase in the age at the first contact with HAV infection.

The epidemiology over the world

The epidemiological shift for HAV infection has been reported in Latin America, Eastern Europe, Poland, the eastern Mediterranean, Southeast Asia and China [3-5, 8, 9]. Although the prevalence of anti-HAV antibodies among children (1-5 years) increased from 1992 to 1998 and from 1998 to 2004 in Tuscany, Italy, the percentage of immune young adults (15-20 years) over time did not show a statistically significant trend with an increased risk for susceptible adolescents and young adults [10]. Over the past 30 years in Korea, the most susceptible age group changed from children aged less than 10 years to young adults aged 20-29 [9].

The epidemiology in Turkey

There are limited data about the epidemiological shift of HAV in Turkey. [1] Reported the change in the seroprevalence in persons between 1 and 60 years old from Izmir, Turkey, in 1998 and 2008. The rate of anti-HAV seropositivity by the age of 10-14 years decreased from 65% to 23% from 1998 to 2008 [1]. The anti-HAV seroprevalence was 4.6% among children aged 1-4 years [1]. Various studies on the epidemiology of HAV infection in Turkey have revealed differences between the regions [1, 11-13]. The seroprevalence rate of anti-HAV was 67.8% in rural areas and 25.8% in urban areas in children under the age of 6 years in Konya, Turkey [11]. The HAV prevalence rate was 19.2% in children 2-5 years old, 74.3% in children 6-10 years old and 83% in children 11-14 years, with an overall prevalence of 57.2%, in the eastern Mediterranean region of Turkey in 2007 [12]. In 2001, the seroprevalence of HAV was 29% in Istanbul, and the prevalence increased from 15.1% in 0- to 5-year-old children to 49.6% in children aged 10-15 years [13]. A recent study from Istanbul detected anti-HAV seropositivity in 11.4% of children 5-9 years old, 29% in children 10-14 years old and 49.7% in children 15-19 years old [14].

Hepatitis A-associated risk factors

Our findings are consistent with those of other studies showing an inverse correlation between HAV seropositivity and SES [1, 11, 14, 15]. However, the interaction was not significant after logistic regression analysis in our study. The anti-HAV seroprevalence was 59.5% in large families with ≥5 members, higher than the seroprevalence in small families with ≤4 members [1]. The total anti-HAV seroprevalence increased with a greater number of siblings: 37.5% with 2 or fewer siblings, 68.3% with 3-5 siblings and 81.2% with 6 or more siblings [12]. The seropositivity was higher in children for whom the number of rooms per individual was lower [14]. In our study, a high in-house population was not a significant factor increasing the risk of anti-HAV positivity. This difference could be related to the different age groups because we studied only children in our study, whereas other studies included adults, who have a higher rate of anti-HAV seropositivity [1].

In countries with high seropositivity, for example Madagascar, 64.6% in 2- to 5-year-olds and 88.2% in 5- to 10-year-olds, age, socioeconomic status, access to clean water and the parents' occupations were found to be significantly associated with seropositivity [15]. In our study, children using tap water as drinking water had the highest rate of seropositivity (15.7%).

Day-care attendance for children under six years old was identified as a risk factor (OR: 4.4, 95% CI, 1.7-11.7) in Ankara. The HAV IgG positivity was reported to be 11.4% in children aged between 4 and 6 years who attended a preschool or a day-care center [16]. This difference is thought to be related to the health conditions, the number of children attending school, the toilet-training status of children and the socioeconomic status of the families. In our study, the anti-HAV seropositivity was highest among children aged between 10 and 18 years, and although the trend was not statistically significant, the rate of seropositivity increased with age.

Seropositivity was not statistically related to the paternal education level [12]. However, as the maternal education level increased, less HAV positivity was recorded [12, 13]. In our study, we did not find a significant relationship between the parental education level and anti-HAV seropositivity. The seropositivity rate was higher in children whose fathers were illiterate (27.3%).

Limitations

One limitation to our study is that the study subjects from the outpatient clinics may not be representative of the whole population of Istanbul, thus limiting the relevance of the results. In Turkey, nearly 23% of the population has a university degree and 21.5% has a monthly income around ≥2000 YTL (Turkey Statistical Institute, OESD Better Life Index). Because of the differences of the seropositivities between cities and the great variations between socioeconomic status, monthly income, education levels, our study results cannot be generalized throughout Turkey. Studies published in the literature differ with respect to the study population, timing, sample size, location, geographic and/or socioeconomic status and kits used for laboratory analysis, and these differences make the comparison of the results impossible.

Strengths

The strengths of our study are that all of the children included in the study were unvaccinated, making the results relevant with no need to account for vaccine-induced antibodies, and that the study showed a dramatic change in the rate of seropositivity at our center over a period of 15 years.

Conclusions

Given the serological shift over time [1, 3-5, 8, 9], greater susceptibility and a persistent risk of exposure to HAV suggest that outbreaks are possible. As the endemicity of HAV infection decreases, the number of susceptible adolescents increases. The Ministry of Health updated the national immunization schedule for children in Turkey and the hepatitis A vaccine has been included in the national immunization program in 2012.

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