

Hepatitis B virus seroprevalence, associated factors and vaccination status among children and adolescents in Black Sea Region of Turkey

Erhan Karaaslan^{1*}, Meryem Cetin²

¹Department of Pediatrics, Medical School of Gaziosmanpasa University, Tokat

²Department of Medical Microbiology, Medical School of Gaziosmanpasa University, Tokat

*Corresponding author: drekaraaslan@gmail.com

⁺Speaker: drekaraaslan@gmail.com

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Abstract- The aim of this study was to determine the prevalence of hepatitis B virus (HBV) serologic markers in children and adolescents and the impact of the vaccination program over the last 9 years. The laboratory records of 10175 children were retrospectively evaluated in children who visited a tertiary hospital, between January 2009 and December 2017. The overall prevalence of HBsAg and anti-HBs were 2.0%, and 69.3%, respectively. HBsAg prevalence increased with age. The carriage rate was more prevalent in rural areas and in cases born before the country-wide vaccination program. HBeAg positive cases were more common than anti-HBe Ag positive cases (67.6% vs. 32.4%). Anti-HBs was on a rising trend in the 1-23-month age group while it tended to decline after 2-6 years' age group.

There was a decrease in the prevalence of HBsAg in children due to ongoing vaccination efforts but the prevalence of HBsAg was still high during adolescence. The rates of anti-HBs positivity were lower in those living in rural areas and those born before the vaccination program. Anti-HBs rates were decreasing as age progressed, but this decline was probably due to a natural reduction in anti-HBs concentration in successfully vaccinated individuals.

Keywords: Hepatitis B, epidemiology, children, vaccination, Turkey

Introduction

Hepatitis B virus (HBV) is a major cause of liver diseases worldwide. More than 2 billion people in the world show evidence of hepatitis B, and 350 million are chronic carriers (1). The World Health Organization reports 240 million chronic infections in middle- and low-income countries and about 650 000 of them die from complications of chronic hepatitis B such as cirrhosis, hepatocellular carcinoma (2). Hepatitis B virus is transmitted by parenteral or mucosal contact of blood and serosal fluids. Chronic infection develops in 90% of infants with maternal hepatitis B infection. In addition, 30% to 50% of HBV infections between 1 and 5 years of age are reported to evolve into chronic infection (3). Turkey

is a medium endemic country; the hepatitis B seroprevalence of Turkey has declined from 20% - 40% to 2% -8% with the universal immunization program implemented in 1998 (4).

The objective of this study was to assess the prevalence of hepatitis B and to contribute to future vaccination strategies by analyzing data collected over an 9-year period.

Materials and Methods

This retrospective cross-sectional study was conducted at outpatient clinics between January 2009 and December 2017 to evaluate the prevalence of HBV serological markers in children and adolescents.

All blood samples were tested using an enzyme-based immunoassay method. HBV DNA was evaluated quantitatively by real-time PCR.

We compared the results using chi-square tests, and chi-square for trend. Mann-Whitney U test was performed because the distribution of continuous variables was not normal. A p value < 0.05 was considered statistically significant. The tests were also performed for each age group. Confidence interval was calculated by using "Wilson" method. EpiTools, and coin libraries of R-software were used for data calculations. All statistical analyses were implemented using R-3.4.1 software ([http:// www.r-project.org/](http://www.r-project.org/), Vienna, Austria).

Results

Hepatitis B virus surface antigen (HBsAg) was recorded from 10175 records, 4823 (47.4%) were female and 5352 (52.6%) were male. The age distribution was as follows: 888 (8.7%) cases between the ages of 1-23 months, 2745 (27.1%) cases between the ages of 2-6 years, 2569 (25.2%) cases between the ages of 7 to 12 years, and 3973 (39%) was between 13-18 years old.

A total of 205 HBsAg-positive tests (2.0%) were detected during the study. HBsAg reactivity by sex,

settlement and age groups are presented in Table 1. HBsAg positivity was 2.0% in males and 2.0% in females and this difference was not statistically significant. The rate of HBsAg positivity was 7.4% in rural areas and 1.3% in urban areas and the difference was statistically significant (p <0.001). The trend of HBsAg positivity with age was statistically significant (p <0.001).

The total number of cases tested for anti-HBs was 6065, of which 4204 (69.3%) were positive for anti-HBs. Anti-HBs positivity was 69.8% in males and 68.8% in females and this difference was not statistically significant. The rate of anti-HBs positivity was 60.7% in rural areas and 70.7% in urban areas, the difference was statistically significant (p <0.001). The rate of anti-HBs positivity was observed to be 85.8% in infants between the ages of 1-23 months, 78.3% in children between the ages of 2-6, 66.9% in children between 7-12 years, and 61.6% in 13-18-years old. The trend to decrease anti-HBs positivity with age was statistically significant (p <0.001). Anti-HBs positivity was found to be 61.3% in those who were born before 1998 and 73.5% in those born after 1998, and there was a statistically significant difference (p <0.001). These data are summarized in Table 1.

Table 1: Prevalence of hepatitis B virus markers according to age, sex and settlement

	HBsAg (+), Anti-HBs (-)			Anti-HBs (+), HBsAg (-)		
	n/N (%)	%95 CI	p	n/N(%)	%95CI	p
Gender						
Female	98 / 4823 (2.0)	1.6-2.4	0.9	2017/2931(68.8)	67.1-70.5	0.4
Male	107 / 5352 (2.0)	1.6-2.4		2187/3134(69.8)	68.1-71.4	
Settlement						
Rural	85 / 1148 (7.4)	5.9-9.0	<0.001	503/829(60.7)	57.2-64.0	<0.001
Urban	120 / 9027 (1.3)	1.1-1.6		3701/5236(70.7)	69.4-71.9	
Birth Years						
Before 1998	131/2848 (4.6)	3.7-5.4	<0.001	1282/2092(61.8)	60.7-64.9	<0.001
After 1998	74/7327 (1.0)	0.7-1.3		2922/3973(73.5)	72.1-74.9	
Age Groups						
1-23 months	3 / 888 (0.3)	0.06-0.9	<0.001*	647/754(85.8)	83.1-88.2	<0.001*
2-6 years	18 / 2745 (0.7)	0.3-1.0		981/1253(78.3)	75.9-80.5	
7-12 years	24 / 2569 (0.9)	0.6-1.4		940/1404(66.9)	64.4-69.4	
13-18 yeas	160 / 3973 (4.0)	3.4-4.7		1636/2654(61.6)	59.8-63.5	
Total	205 / 10175 (2.0)	1.7-2.3		4204/6065(69.3)	68.1-70.5	

* chi-square for trend

The rates of HBsAg seropositivity were around 2.4% between 2009 and 2012, but were up to 3.6% in 2012. In the following years, seroprevalence rate gradually decreased from 3.6% in 2012 to 0.9% in 2017, and the trend of HBsAg positivity was statistically significant ($p < 0.001$). HBsAg seropositivity trends are summarized in Table 2.

Table 2: HBsAg seropositivity trends over years by age groups (n/N(%))

Years	1-23 months	2-6 years	7-12 year	13-18 years	Total
2009	2/145(1.4)	3/243(1.2)	3/275(1.1)	18/408(4.4)	26/1071(2.4)
2010	1/141(0.7)	3/300(1.0)	2/314(0.6)	23/517(4.4)	29/1272(2.3)
2011	0/81(0)	3/219(1.4)	5/276(1.8)	15/411(3.6)	23/987(2.3)
2012	0/112(0)	4/250(1.6)	5/257(1.9)	30/452(6.6)	39/1071(3.6)
2013	0/96(0)	2/281(0.7)	2/247(0.8)	28/496(5.6)	32/1120(2.9)
2014	0/127(0)	2/341(0.6)	1/276(0.4)	19/542(3.5)	22/1286(1.7)
2015	0/106(0)	1/303(0.3)	3/348(0.9)	12/470(2.6)	16/1227(1.3)
2016	0/57(0)	0/435(0)	2/343(0.6)	8/462(1.7)	10/1297(0.8)
2017	0/31(0)	0/392(0)	1/233(0.5)	7/215(3.3)	8/844(0.9)
Total	3/888(0.3)	18/2745(0.7)	24/2569 (0.9)	158/3971(4.0)	203/10175(2.0)
p*	<0.05	<0.05	0.2	<0.05	<0.001

*chi-square for trend

Other risk factors obtained from patient files are given in Table 3.

Table 3: Other risk factors for HBsAg positivity

	n	%
Only mother HBsAg positive	22	10.7
Only father HBsAg positive	3	1.5
Only a sibling positive	33	16.1
Both father and a sibling	10	4.9
Both mother and a sibling	29	14.1
All household	8	3.9
A relative positive	2	1.0
Operation history	11	5.4
Dental operation	1	0.5
Sexual contact	1	0.5
Blood transfusion	3	1.5
No Risk	77	37.6

Demographic and laboratory analysis results of HBeAg and anti-HBe positive infections are given in Table 4.

Table 4: Demographic and laboratory characteristics in HBeAg and anti-HBe immunoglobulin positive infections

	HBeAg (+)	Anti-HBe (+)	p
Age (n:117 / 56; year; mean \pm SD)	14.1 \pm 4.0	14.2 \pm 4.4	0.3
Gender (female / male; n:79 / 94)	%49.6 / %50.4	%7.5 / %62.5	0.1
ALT (n:104 / 53; IU mL ⁻¹ ; mean \pm SD)	54.9 \pm 54.9	44.9 \pm 56.1	<0.05
AST (n:104 / 52; IU mL ⁻¹ ; mean \pm SD)	41.3 \pm 35.3	34.7 \pm 23.3	0.2
HBV DNA (n:104 vs 62; IU mL ⁻¹ . mean)	5.4x10 ⁸	1.1x10 ⁸	<0.05

ALT: alanine amino transferase. AST: aspartate amino transferase

Discussion

The prevalence of HBsAg in rural regions (7.4%) is significantly higher than that in urban regions (2.0%). The prevalence in infants (1-23 months age group) was 0.3%. Despite the prevalence of HBsAg had a

declining trend over the years in adolescents; the rate was still high (4.0%).

The epidemiological studies indicate that the incidence of hepatitis B infections has decreased both

in the world and in Turkey. In a report, the studies of viral hepatitis published over a 27-years period between 1980 and 2007 showed that worldwide chronic HBV infection decreased in the 1990-2005 period. Despite this decline, Turkey is still among the moderate endemic countries (4). We found an overall HBsAg-positivity rate of 2.0% during the study period. HBsAg positivity rates have been decreasing since 2012, and declined significantly to 0.9% in 2017 ($p < 0.001$).

The seroprevalence of HBV was reported 9.7% in children in the eastern region of Turkey in 2003 (5). In a more developed region of the country, the HBsAg seroprevalence was found to be 2.8% in individuals younger than 20 years (6). In our study, carrier rate in the age group of 1-23 months was found 0.3%, similarly, the rate was 0.7% in the age of 2-6 years groups and 0.9% in 7-12 years ages group. However, despite the significant declines observed in the 13- 18 age group, the overall prevalence was still high at 4.0%.

In this study, HBsAg positivity rate was 1.4% between 1-23-month-old children in 2009 and decreased to 0% in 2017 ($p: 0.03$), that showed the protection measures in the infants of infected mothers were applied timely and adequately in our region.

The horizontal transmission of HBV is also common in medium endemic regions. The majority of HBV are acquired in childhood and early adulthood, and HBV seroprevalence in late childhood is close to the rate seen in adults (3). The prevalence of HBsAg carriers in our study was observed to change every year towards older age groups. HBsAg rates in this study were significantly higher in the 13-18 age group between 2009- 2012, but the rates have declined steadily over the following years. In our study, no statistically significant difference was found between males and females in terms of HBsAg-positivity.

In Turkey, HBsAg seropositivity was more common in rural areas in 1995 (5). Seroprevalence of HBsAg were investigated in rural and urban regions of four provinces in south-eastern Anatolia in 2004, and the prevalence of HBsAg was 8.2% in rural areas and 6.2% in urban areas in adults (7). The seropositivity in rural areas was found higher than that in urban areas in our study.

Especially in the endemic areas, the importance of vertical transfer as well as the horizontal transfer in the spread of HBV infection among family members has been reported.

The HBeAg positive stage is known to exhibit an early stage of infection with higher levels of viral activity (hepatic enzymes and HBV DNA increase) as compared to anti-HBe positive stage (8). The comparison of HBeAg and anti-HBe positive individuals in this study revealed that the mean ALT and HBV DNA levels were higher in HBeAg positive patients. This confirms the above-mentioned tendency. HBeAg-positive subjects had more HBV-DNA counts.

The seroprevalence of anti-HBs in Turkey in 1998 was reported to be 17% (5) and was reported to be 30% in 2008 (9). According to data from the Ministry of Health of Turkey, the vaccination coverage has increased to 90% since 2005 (7). In this study, immunization rates for the 1-23-months age group increased every year and reached 94.1% in 2017, confirming the data above. One study showed that serum anti-HBs concentration in successfully immunized infants during the first 2 years dropped to less than 10 IU / ml, but none of the children developed HBsAg-positive or symptomatic infection during an 18-year follow-up period (10). In our study, anti-HBs positivity decreased with increasing age. In this study, anti-HBs positivity rates decreased from 85.8% in the age group of 1-23 months to 61.6% in the 13-18 age group and this result supported other studies; as mentioned above, we consider that the reason for this is a natural decline.

In conclusion, it is important to evaluate the extent of the problem of HBV infection in each region of the country. The findings of this study revealed the epidemiological characteristics of hepatitis B in children in the northern Turkey. Finally, universal HBV vaccination, which has been in use for 19 years in our country, has significantly reduced HBsAg positivity especially during childhood, and therefore newborn vaccination should be continued with high vaccination coverage rates.

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