The prevalence of atopy in children with antibodies against hepatitis A virus and hepatitis B virus

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To investigate the relationship between atopy and hepatitis A virus (HAV) and hepatitis B virus (HBV) infections, we studied 42 children who had had HAV infection (Group I), 28 children who had had HBV infection (Group II), and 31 children who were seronegative for both HAV and HBV infection (Control group). Serological tests for HAV and HBV infections (anti-HAV IgG, HBsAg, anti-HBc IgG) and allergic skin tests and specific IgE investigations for the detection of atopy were carried out.

In this study, there was no significant divergence in the socio-demographic characteristics among the three groups. The rates of specific IgE positivity in children in the HAV seropositive group (11.9%) and in children in the HBV seropositive group (17.8%) were lower than in the control group (35.4%) ($p=0.03$ and $p=0.22$, respectively). Also, the number of children with respiratory allergic diseases (allergic rhinitis and/or asthma) both in the HAV seropositive group and in the HBV seropositive group were significantly lower than in the control group ($p<0.05$). When atopy in all of the groups was evaluated, the prevalence of atopy was found to be more widespread in HAV seronegative children (Adjusted OR, 9.2; 95% CI, 1.7-48.2) and HBV seronegative children (Adjusted OR, 5.9; 95% CI, 1.1-31.8) than in HAV and HBV seropositive children, after adjustment for age, number of older siblings and education of the father.

In conclusion, in this study, the prevalence of atopy in children who had had HAV or HBV infection was found to be low, and this situation was considered to be related to the relationship of HAV and HBV infections to poor hygiene and to the fact that these infections occur at early ages in Turkey.

Key words: *atopy, hepatitis A, hepatitis B, childhood.*

For the past 20 years, the prevalence of atopic diseases such as asthma, allergic rhinitis, and atopic dermatitis has been increasing in developed countries[1,2]. According to the hygiene hypothesis, there is a close relationship between improvement in public health and hygienic conditions and an increase in atopic diseases. Thus, the main factor in the increase in atopic diseases in western countries is a decrease in bacterial and viral infections during childhood. Accordingly, the decrease in the Th1 immune response to microorganisms leads to the clonal development of specific Th2 lymphocytes resulting in the development of allergic diseases[3]. However, it still remains unclear as to whether microbial or non-microbial factors, or perhaps a combination of these, are responsible for the rise in atopy[4].

Studies have shown that the risk of atopic diseases decreases with increasing number of siblings, daycare attendance early in life, exposure to tuberculosis and viral infections during early childhood, and exposure to orofecal/food-borne infections (such as hepatitis A, Toxoplasma gondii and Helicobacter pylori)[4-6]. Recent studies have reported findings supporting the view that a significant factor underlying the allergy and asthma epidemic is a declining exposure to

orofecal and food-borne microbes[7,8]. Atopic diseases result from interactions between genetical tendencies and environmental factors. The type, age, duration and intensity of exposure to environmental factors including infections may affect this interaction for better or worse[9,10]. This situation may lead to different results from the genetic-environmental interactions under different social and cultural conditions and in different countries[11,12].

Studies in various regions of the world such as southern Europe (Italy), northern Europe (Denmark) and North America have shown that there is a negative relationship between hepatitis A viral (HAV) infection and atopic diseases[5,13-15]. In contrast, a limited number of studies done in developed countries did not detect a similar relationship between hepatitis B viral (HBV) infection and atopy[15]. In contrast with western countries, Turkey has a lower prevalence of atopic diseases but has a widespread occurrence of orofecal/food-borne infections[16-18]. In addition, Turkey is a moderate endemic region in regard to HAV and HBV infections, and these infections are acquired during early childhood. The aim of this study was to investigate the prevalence of atopy in children who had had HAV and HBV infections and to determine the relationship between these infections and atopy under the conditions found in Turkey.

Material and Methods

Study Groups: This study included all children who had been diagnosed with acute hepatitis A and B in the last three years in the outpatient clinic of the Department of Pediatric Infectious Diseases of Çukurova University Medical School and who had been found to have recovered on follow-up. Also, all healthy children who presented for hepatitis A and B vaccination in the outpatient clinic of the Department of Pediatrics in the last year and who had been found to be seronegative for hepatitis A and B with screening tests were investigated.

All children found to be infected with acute hepatitis A and B in the last three years were determined from the hospital records, and letters were sent to their families requesting that the children take part in the study. The number of children whose families agreed to their taking part in the study was as follows: 42 (87.5%) of 48 children with HAV infection and 28 (90.3%) of 31 children with HBV infection. Of the families of 34 healthy children seronegative for both HAV and HBV, 31 (91.2%) agreed to their children's taking part in the study.

Information obtained from either or both parents of the children taking part in the study was used in filling out questionnaires. The information included the ages and gender of the children, number of siblings, area of residence, the educational level of the fathers, smoking in the family, family history of respiratory allergic diseases (asthma and rhinitis), infectious diseases (chicken pox, measles and mumps) of the children acquired between 0-2 years of age, and vaccinations during childhood. Later, blood samples were taken from all the children to investigate the presence of antibodies against HAV and HBV and the sera were stored at -20°C. Allergic skin tests and detection of specific IgE were carried out on all of the children and all were evaluated for the presence of respiratory allergic diseases by the Department of Pediatric Allergy. This study was approved by the Ethics Commission of the Çukurova University Medical School.

Serological tests: Tests for hepatitis B surface antigen (HBsAg) and total serum antibodies against hepatitis A virus (Anti HAV IgG) and hepatitis B core antigen (Anti-HBc IgG) were done using the microparticle-enzyme immunoassay (MEIA) method (Abbott Laboratories, USA) on the sera of all the children. The positive and negative results of the tests were evaluated according to the recommendations in the kit used. Anti HAV IgG positivity was accepted as evidence of past hepatitis A infection and anti-HBc IgG positivity of a past hepatitis B infection.

Skin Prick Test (SPT): Allergy SPTs (Allergopharma, Reinbeck, Germany) were performed on the forearm of each child. The tested allergens were tree I and II mixes, grass mix, grass-cereal mix, mold I and II mixes, mites (Dermatophagoides farinea and Dermatophagoides pteronyssinus), cow's milk, egg white, peanut, wheat, cat epithelia, dog epithelia and sheep's wool. Histamine (10 mg/ml) was used as the positive control and normal saline as the negative control. A SPT result was considered positive if the wheal diameter was 3 mm or larger after subtraction of the wheal diameter of the negative control after 15 minutes. Children with at least one positive SPT were considered to be atopic.

Specific Serum IgE: Specific serum IgE was determined by RAST (Pharmacia&Upjohn AB, Uppsala, Sweden) in accordance with the recommendations of the manufacturer. A RAST value of >0.35 kU/L was considered positive. The following antigens were tested: food mix (nuts, cereals and pediatric), house dust mix, mold mix, animal mix, weed mix and tree mix.

Diagnosis of allergic rhinitis and asthma: All children were evaluated in the Department of Pediatric Allergy for the presence of allergic rhinitis and asthma. If the mother and/or father answered "yes" to one or both of the questions, "Has a doctor ever told you that your child had asthma and/or hay fever?" and "Does your child still have asthma and/or hay fever?" and if the skin tests were positive the child was accepted as having allergic asthma or rhinitis.

Description of variables: If the mother or father of a child answered the questions "Has a doctor ever told you that you, your mate or your other children had asthma and/or hay fever?" and "Do you, your mate or your other children still have asthma or hay fever?" with a "yes", the family was considered to have a history of respiratory allergic disease.

Children who lived in areas with a population over 10,000 were considered to be living in an urban area and those living in areas with a population below 10,000 in a rural area. A home where for the last six months at least one cigarette a day was smoked by the mother, father or another member of the family was considered to be a smoking family. Education was evaluated according to whether the fathers had completed primary, middle or high school or university. If the vaccines for the first year of life recommended by the Health Ministry of the Republic of Turkey had all been given, the children were considered to be completely vaccinated.

Statistical evaluation: The data obtained in this study were evaluated using the SPSS Version 12. Differences in groups of categorical variables and the relationship of HAV/HBV seropositivity with skin tests and specific IgE with respiratory allergic diseases were analyzed using chi-square tests. The degree of association between factors and disease is expressed as the odds ratio (OR) with the 95% confidence interval (95% CI). Before defining factors that affected the risk of atopy, univariate analysis was carried out. The effect of various risk factors on atopy along with their results was evaluated using multivariate logistic regression analysis. A value of $p < 0.05$ was considered as significant.

Results

In this study, 42 healthy children who had been infected with hepatitis A (HAV) (Group I) and 28 healthy children who had been infected with hepatitis B (HBV) (Group II) along with a control group of 31 healthy children who were seronegative for both HAV and HBV were investigated. All of the children who had had HAV infection were HBV seronegative and all of the children who had had HBV infection were HBsAg negative and HAV seronegative. There was no significant statistical difference among the children in Group I, Group II or the control group regarding their average age, male/female ratio, the area where they lived, their fathers' educational level, the number of smokers in the family, childhood diseases (chicken pox, measles, mumps) between ages 0-2 years, vaccinations during childhood and the number of older siblings ($p>0.05$) (Table I).

When the HAV seropositive group (Group I) was compared with the HAV seronegative group (Control), it was found that there was no significant difference in the family history of allergic diseases (allergic rhinitis and asthma) between the two groups. However, the difference in the prevalence of atopy between the groups was found to be significant, with the atopy prevalence in the HAV seropositive children being 4.8% and in the HAV seronegative group, 32.2% ($p=0.006$) (OR, 9.52; 95% CI, 1.9-47.5) (Table II). Similarly, the rate of specific IgE positivity in children in the HAV seropositive group was significantly lower (11.9%) than that in the HAV seronegative group 35.4% ($p=0.03$) (OR, 4.07; 95% CI, 1.1-15.9). In addition, rates of respiratory allergic diseases (allergic rhinitis and/or asthma), sensitivity to more than two allergens and sensitivity to mites in house dust in children in the HAV seropositive group were significantly lower than in the HAV seronegative group.

When the HBV seropositive group (Group II) was compared to the HBV seronegative group (Control), it was found that there was no

Table I. Demographic Characteristics of HAV Seropositive Children (Group I), HBV Seropositive Children (Group II) and Children Seronegative for Both Infections (Control Group)

	HAV seropositive (Group I) (n:42)	HBV seropositive (Group II) (n:28)	Seronegative (Control Group) (n:31)	(p)
Age (in years)				
Mean (± SD)	8.5±2.1	8.3±2.3	8.6±2.4	NS
(Min-Max)	(4-12)	(3-12)	(4-13)	
Gender (Male/female)	27/15	18/10	17/14	NS
Place of residence (n, %)				NS
Urban	40 (95.2)	26 (92.8)	29 (93.5)	
Rural	2 (4.8)	2 (7.2)	2 (6.5)	
Educational level of father (n, %)				NS
Primary school	2 (4.8)	1 (3.6)	2 (6.5)	
Middle school	6 (14.3)	5 (17.9)	2 (6.5)	
High school	11 (26.2)	6 (21.4)	14 (45.2)	
University	23 (54.8)	16 (57.1)	13 (41.9)	
Smokers in family (n, %)				NS
Mother only	5 (11.9)	3 (10.7)	4 (12.9)	
Father only	8 (19.0)	5 (17.8)	6 (19.3)	
Both	4 (9.5)	2 (7.2)	3 (9.7)	
None	25 (59.6)	18 (64.3)	18 (58.1)	
History of childhood infections (n, %)				NS
Chickenpox (+)	12 (28.6)	8 (28.6)	11 (42.3)	
Measles (+)	3 (7.1)	2 (7.1)	3 (11.5)	
Mumps (+)	6 (14.3)	3 (10.7)	4 (15.7)	
Chickenpox and mumps (+)	2 (4.8)	2 (7.1)	3 (11.5)	
Number of older siblings (n, %)				NS
1	17 (40.5)	8 (28.6)	9 (29.0)	
≥2	5 (11.9)	5 (17.8)	6 (19.3)	
Vaccinations during childhood (+) (n, %)	41 (97.6)	27 (96.4)	31 (100)	NS

Table II. Atopy and Atopic Diseases in HAV Seropositive, in HBV Seropositive and in HAV/HBV Seronegative Children

Characteristics	HAV seropositive (Group I) (n:42) n (%)	HBV seropositive (Group II) (n:28) n (%)	HAV/HBV seronegative Control Group (n:31) n (%)	Odds ratio (A) (95%Cl)	Odds ratio (B) (95%Cl)
Skin prick test (+)	2 (4.8)	2 (7.1)	10 (32.2)	9.52 (1.9-47.5)**	6.19 (1.22-31.4)*
Specific Ig E (+)	5 (11.9)	5 (17.8)	11 (35.4)	4.07 (1.1-15.9)*	2.53 (0.65-10.21)
Respiratory allergic disease					
Allergic rhinitis (± asthma)	1	0	4	6.07 (0.58-150.84)	–
Allergic asthma (± rhinitis)	1	1	4	6.07 (0.58-150.84)	4.00 (0.37-100.45)
Total (allergic rhinitis and/or asthma)	2	1	8	6.96 (1.20-52.23)*	9.39 (1.04-15.38)*
Number of allergens sensitive to					
1	1	1	4	6.07 (0.58-150.84)	4.00 (0.37-100.45)
>2	1	1	6	9.84 (1.06-229.98)	6.48 (0.68-153.15)
At least 1	2	2	10	9.52 (1.70-69.79)**	5.20 (0.92-38.36)
Prevalence of sensitization to allergens					
1. Mites	1	1	6	9.84 (1.06-229.98)*	6.48 (0.68-153.15)
2. Mixed tree pollens	1	0	2	2.83 (0.19-82.97)	–
3. Mixed grass pollens	0	1	2	–	1.86 (0.12-55.25)
Family history of allergic diseases (+)	16 (38.1)	9 (32.1)	12 (38.7)	1.03 (0.35-2.96)	1.33 (0.40-4.48)

A : Comparison between Group I and Control Group. Odds ratio (A) indicates risk of atopy among HAV/HBV negative when compared to HAV positive.

B : Comparison between Group II and Control Group. Odds ratio (B) indicates risk of atopy among HAV/HBV negative when compared to HBV positive.

*: $p<0.05$, **: $p<0.01$

significant difference in the two groups in the family history of allergic disease. However, the prevalence of atopy in the HBV seropositive children was significantly lower (7.1%) than in the HBV seronegative group (32.2%) (OR, 6.19; 95% CI, 1.22-31.40) (Table II). Also, the number of children with respiratory allergic diseases (allergic rhinitis and/or asthma) in the HBV seropositive group was lower than in the HBV seronegative group (p=0.03). In contrast, even though the rates of specific IgE positivity, sensitivity to more than two allergens and sensitivity to mites were lower in the children in the HBV seropositive group than in the HBV seronegative group, the difference was not significant (p>0.05).

All of the children in the study (Group I, Group II and the control group) were evaluated for the development of atopic sensitivity according to HAV seropositivity, HBV seropositivity and several social-demographic variables (age, father's educational level, and number of older siblings) using multivariate analysis (Table III). According to this, after adjustment for socio-demographic factors such as age, father's educational level, and number of older siblings, children who were seronegative for both HAV and HBV were more likely to be affected by atopic sensitization than those who were seropositive for HAV (OR, 9.2; 95%CI, 1.7-48.2) and those who were seropositive for HBV (OR, 5.9; 95%CI, 1.1-31.8).

Discussion

In this study, it was found that there was a reverse relationship between the presence of antibodies against hepatitis A virus (Anti HAV IgG) and hepatitis B virus core antigen (Anti HBc IgG) and the prevalence of atopy (positivity of skin tests against respiratory allergens) and respiratory allergic diseases (allergic rhinitis and asthma) in children aged 3-13 years and that this characteristic was not affected by such factors as age, father's educational level, and number of older siblings.

Before evaluating the findings, certain methodological restrictions must be taken into consideration, namely that this study is a cross-sectional study, it was carried out on children seen in the hospital, the number of children in the study is low, and some of the data about the children was obtained from the parents. On the other hand, this study differs from studies carried out in western countries in that in Turkey, hepatitis A and B infections are widespread; the life style, dietary habits, and climate are different; the subjects in the

Table III. Skin Sensitization to Common Airborne Allergens in All 101 Children Studied According to Presence of Antibodies to Hepatitis A Virus, Hepatitis B Virus and to Relevant Sociodemographic Factors

	Frequency of atopy (n%)		Crude Odds Ratio (95%CI)	(p)	Adjusted Odds Ratio (95%CI)	(p)
Antibody to hepatitis A virus						
Positive	(n:42)	2 (4.8)	1.0			
Negative	(n:59)	12 (20.3)	5. 1 (1.1-24.2)	0.04	9.2 (1.7-48.2)	0.009
Antibody to hepatitis B virus						
Positive	(n:28)	2 (7.1)	1.0			
Negative	(n:73)	12 (16.4)	2.6 (0.5-12.2)	0.24	5.9 (1.1-31.8)	0.038
Age (in years)						
≤ 7 years	(n:33)	4 (12.1)	1.0			
> 7 years	(n:68)	19 (14.7)	1.3 (0.4-4.3)	0.73	1.4 (0.4-5.4)	0.63
Father's education						
Primary school	(n:18)	3 (16.7)	1.0			
High school	(n:31)	6 (19.4)	1.2 (0.3-5.5)	0.82	0.7 (0.12-3.75)	0.65
University	(n:52)	5 (9.6)	0.5 (0.1-2.5)	0.42	0.4 (0.06-2.35)	0.29
Presence of older siblings						
Yes	(n:50)	7 (14.0)	1.0			
No	(n:51)	7 (13.7)	1.0 (0.3-3.2)	0.97	1.3 (0.32-5.6)	0.69

study were pre-pubertal (3-13 years of age); and it was possible to investigate the effect of early acquired hepatitis A and B infections on the development of atopy in these conditions using objective tests (such as allergic skin tests, specific IgE, and serologic tests).

The studies carried out in various western countries (Italy, Denmark and the United States) show that there is a negative relationship between HAV infection and allergic diseases[5,13-15]. Our study showed that atopy, specific IgE positivity and allergic diseases (allergic rhinitis and asthma) were seen less in children with IgG antibodies against HAV. This relationship was unrelated to age, father's level of education or number of older siblings.

Both the findings of studies published in western countries and those of our study support the hygiene hypothesis. It was thought that hepatitis A infection was not causally linked to less allergy, but just a reliable proxy ofexposure to more orofecal/food-borne infections[19,20]. A recent study has shown that HAV positive persons who have a special variant of a gene that encodes TIM-1, the human cell surface receptor for HAV, are less likely to develop atopy[21]. According to this, CD4 T cells express TIM-1 during the activation and differentiation for the Th2 responses. For this reason, HAV may directly inhibit Th2 differentiation by binding to TIM-1. It has been suggested that the genetical interaction between HAV and TIM-1 is the first molecular-genetical proof for the hygiene hypothesis, and it has been proposed that the HAV could have a direct effect on Th1/Th2 differentiation or on Th2 survival[22]. No investigation of the mechanism of the relationship between hepatitis A infection and atopy was made in this study.

Prior to 1970, the seroprevalence of antibodies to HAV approached 100% in western countries, and in recent decades anti-HAV seroprevalence rates have fallen to 25-30%, while atopic disease prevalence has doubled[23]. In western countries, each of the factors related to HAV seropositivity such as poor hygienic conditions, large family size and attendance at daycare have a negative relationship on atopy. Studies carried out in Turkey have shown that the anti-HAV seroprevalence rate in the 0-18 age group varies between 73-97%, and that the rate varies between 92-99% at 20 years of age and over. It was also shown that hepatitis A infection is closely related to poor hygienic conditions[17]. In contrast to this, the prevalence of asthma in children in Turkey is between 4-6%[16]. Since there are no data in regard to variations in the prevalence of atopy and the extent of hepatitis A infection in Turkey in the past years, it is difficult to interpret the relationship of the prevalence of asthma and hepatitis A infection at an epidemiological level.

We were able to find only one study in the literature whose aim was to investigate the relationship between hepatitis B infection and atopy[15]. This study was carried out on a large national sample in the U.S., and a negative relationship was found between hay fever, asthma and positivity of skin tests against several respiratory allergens, and HAV, T. gondii and herpes simplex virus (HSV)-1 infections. However, a similar relationship was not found between atopy and HBV or HCV infections. The authors suggested that this was due to the fact that HAV, T. gondii and HSV-1 occur early in life, while HSV-2, HBV and HCV infections are acquired after puberty. According to the authors, this finding showed that the earlier certain infections are acquired, the stronger their putative protecting effects.

Our study showed that there is a reverse relationship between the presence of hepatitis B viral antibody (Anti HBc IgG) with atopy and respiratory allergic diseases (allergic rhinitis and/or asthma). This characteristic was not affected by age, father's level of education or number of older siblings. To our knowledge this is the first study to report a negative relationship between hepatitis B infection and atopy; therefore, further studies are warranted.

It has been reported that in the city of Adana, where the present study was carried out, the rate of HBsAg positivity in the 4-7 age group is 5.4%; in the 8-11 age group, 11.4%; and in the 12-15 age group, 11.9%[24]. These values show that in regard to HBV infection, Turkey has a moderate endemicity. In western countries, HBsAg positivity is less than 2% and infection is usually acquired in adulthood by parenteral and sexual contact. In moderate endemicity areas such as in Turkey, HBV infection usually occurs during early childhood and is acquired horizontally, and infection usually occurs in families with a low socio-economic level living

under crowded and poor hygienic conditions[18]. Under these conditions, necessities such as towels, tooth brushes, razor blades, scissors or manicure-pedicure sets are used in the family, or at the barber or hairdresser, without being well sterilized, leading to spread of infection. Also, widespread kissing and contact between children at play also contributes to the spread. In contrast to the study made in the U.S., in our study the negative relationship between HBV infection and atopy and allergic diseases may be due to the fact that HBV infection is often acquired during early childhood and related to poor hygienic conditions.

The mechanism by which the development of atopy is inhibited by HBV infection in children is unknown. CD8 T cells along with interferon-gamma and tumor necrosis factor (TNF)-alpha, which have a role in the recovery from hepatitis B infection, may also play a role in the inhibition of atopy by modifying the balance of Th1/Th2 and/or affecting the regulatory T lymphocytes[25,26].

In conclusion, this study showed that the prevalence of atopy and allergic diseases was lower in children who had acquired hepatitis A and hepatitis B infections. This situation was considered to be due to a relationship between hepatitis A and hepatitis B infections and poor hygienic conditions as well as to the acquirement of these infections at an early age in Turkey. However, it will be necessary to carry out prospective studies in larger groups in populations with different epidemiological characteristics regarding hepatitis B infection, in order to clarify the relationship between hepatitis B infection and atopy.

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