

Atopy in children with chronic hepatitis B virus infection

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Abstract

Aim: To investigate whether immune responses against chronic HBV infection in children have an effect on prevalence of allergic diseases and atopy.

Methods: Children with chronic HBV infection [HBV carriage (group 1) and chronic hepatitis (group 2)] were screened for allergic diseases. The results were compared with age-matched controls (group 3).

Results: The frequencies of doctor-diagnosed 'asthma', 'allergic rhinitis' and 'eczema' were 29.4%, 7.8% and 7.8% in group 1; 7.8%, 5.2% and 5.2% in group 2 and 12.4%, 9% and 2.8% in group 3, respectively. 'History of ever wheezing', doctor-diagnosed 'asthma' and 'eczema' were more common in group 1 than group 3 ($p < 0.05$ for all parameters), and 'history of ever wheezing' and 'doctor-diagnosed asthma' were more common in group 1 than group 2 ($p < 0.05$ for all parameters). Atopy was more common in group 1 (35.2%) than both groups 2 (15.7%) and 3 (18%) ($p < 0.05$ for all parameters). Vertical transmission was more common in patients with versus without atopy in HBV carrier group (33.3% vs. 9%, $p < 0.05$).

Conclusion: Immune responses in chronic HBV infection associated with carrier state may also lead to allergic diseases, which suggests the necessity of following these patients for the allergic diseases along with their viral reactivation.

INTRODUCTION

Hepatitis B virus (HBV) is one of the most common infectious diseases, with an estimated 400 million chronic HBV carriers and 5 million acute infections annually (1,2). It is more prevalent in Asia-Pacific countries and rare in Western countries (2,3). Turkey is in the intermediate region with 4.19% of healthy blood donors reported to be hepatitis B surface antigen (HBsAg) positive (4). HBV is a noncytopathic virus, and cell-mediated immune response directed against the virus is thought to be responsible for the liver injury, which may result in chronic hepatitis, cirrhosis, hepatocellular carcinoma and death (5). Apart from these liver diseases, HBV may also be associated with nephropathy and polyarteritis nodosa, as well as various neurological, dermatological and rheumatologic manifestations (6).

Allergic diseases such as asthma, rhinitis and dermatitis are becoming more widespread in Western countries due to the sanitization of foods, environmental changes, reduced exposure to early childhood viral infections and widespread use of vaccines and antibiotics. The increase in allergic diseases was reconciled with the hygiene hypothesis that was first described by Strachan in 1989 (7). The immune basis of the hygiene hypothesis is explained by two subsets of CD4⁺ T helper (Th) cells, Th1 and Th2. Th1 cells produce interferon- γ , interleukin (IL)-2 and tumour necrosis factor- β , and are mainly involved in delayed hypersensitivity reactions, intracellular infections and autoimmune diseases. On the other hand, Th2 cells produce IL-4, IL-5, IL-10 and IL-13, which are responsible for extracellular infections and IgE-mediated allergic diseases (8). Balance between these two subsets of

CD4⁺ Th cells directs the immune response from one pathway to the other. According to this hypothesis, some viral infections such as measles and hepatitis A, *Toxoplasma gondii*, *Helicobacter pylori*, gastrointestinal infections and tuberculosis may inhibit the allergic diseases by stimulating the Th1 response, whereas some viral infections such as respiratory syncytial virus may promote the allergic diseases by preventing Th1 response (9). Additionally, it was shown that Th1-type immune response is dominant in some chronic diseases such as Hashimoto's thyroiditis, multiple sclerosis, rheumatoid arthritis, Crohn's diseases, sarcoidosis, familial Mediterranean fever and type 1 diabetes mellitus, and thus lower prevalence of allergic diseases is expected in patients with these diseases (9,10).

Although associations of HBV with some dermatological diseases such as lichen planus and popular acrodermatitis have been defined, to date no data have been reported about the association of chronic HBV infection with atopic dermatitis, asthma, allergic rhinitis and atopy (6,11). We therefore aimed to investigate whether or not chronic HBV infection in children, with asymptomatic HBV carriage or chronic HBV hepatitis, has any effect on allergic diseases and atopy.

PATIENTS AND METHODS

Study group

The study consisted of 89 children with chronic HBV infection who were being followed in the paediatric gastroenterology, hepatology and nutrition unit. They were divided into two groups. Group 1 included 51 HBsAg carrier

children, based on the presence of HBsAg in serum for at least 6 months, presence of hepatitis B e (HBe) antibody, absence of HBsAg antibody alanine aminotransferase (ALT) levels within the normal limits (<40 IU/L) and absence of HBV DNA. Group 2 included 38 children with chronic HBV hepatitis, based on the presence of HBsAg in serum for at least 6 months, with presence of HBeAg, absence of HBsAg antibody, ALT levels of more than 1.5 times the normal upper limit and presence of HBV DNA. None of the children in group 2 had laboratory or clinical features of chronic liver disease such as ascites, hepatosplenomegaly or esophageal varices, or hepatocellular carcinoma screened by alpha-feto protein and radiological examination. None of the subjects in either group had history of use of any nucleoside analogues or INF- α for the treatment of their diseases or previous use of antihistamines or corticosteroids within the last 6 months. They were also negative for coinfections with hepatitis C virus (HCV), hepatitis δ virus or HIV, and had no history of chronic liver disease or other chronic diseases. In hepatology unit, all the family members were routinely tested for serological markers of HBV in order to determine possible transmission (vertical or horizontal).

Schoolchildren aged 10–12 years were targeted as the control group (group 3) and six primary schools were randomly chosen by the computer. Subjects with known chronic diseases (diabetes mellitus, malignancy, immune deficiency, chronic liver diseases or chronic renal failure, etc) or with chronic HBV or HCV infection were excluded, and 250 students were chosen randomly. Two hundred nine subjects (83.6%) accepted to participate in the study. All were negative for HBsAg. Demographic and clinical features of the patient and control groups are shown in Table S1.

All the patients and subjects in the control group were questioned about allergic diseases, such as asthma, allergic rhinitis and atopic dermatitis, using the International Study of Asthma and Allergies in Childhood (ISAAC) phase II questionnaire, which was previously validated for the Turkish population (10,12,13). Parents were asked if a doctor had ever diagnosed asthma, hay fever or eczema in their child. Children were defined as having asthma, allergic rhinitis or atopic dermatitis if the diagnosis was previously made by a doctor. The questionnaire included questions about current wheezing, ever wheezing and night cough. Current wheezing was defined as wheezing occurred within the past 12 months. All face-to-face interviews and allergy investigation were performed by two doctors (F.O and M.C).

The study was approved by the Karadeniz Technical University ethics committee, and a written informed consent was obtained from all participants' parents. The study was supported by the Research Fund of Karadeniz Technical University.

Laboratory investigations

Levels of total serum IgE (Dr. Focke, Neuss, Germany) were measured in all patients and in a randomly selected subgroup of 100 children from the healthy subjects. Skin prick test was then performed including 10 common allergens: *Der-matophagoides pteronyssinus* (Dp), *D. farinea* (Df), grass

mix, weed mix, tree mix, *Alternaria*, *Cladosporium*, cockroach, cat dander and hazel nut (Allergopharma, Reinbeck, IA). Histamine and 0.9% NaCl were used as positive and negative controls, respectively. Children with a wheal reaction of ≥ 3 mm, after subtraction of the reaction from negative control, to one or more of the allergen tested, were considered to be atopic.

HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HDV, anti-HCV, and anti-HIV were measured by enzyme immunoassay (Abbott Laboratories, Chicago, IL). The HBV-DNA levels were determined by a hybrid capture assay (Digene, Gaithersburg, MD).

Statistical method

For statistical evaluation, we used SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). Chi-square test and unpaired Student's *t*-test were used for comparing variables of the groups, whereas Mann-Whitney U-test was used as a nonparametric test for analysing the risk factors for atopy.

RESULTS

There were no significant differences between the three groups in terms of age, gender and socioeconomic status. There was also no significant difference in duration of HBsAg positivity and mode of transmission between HBV carrier patients and those with chronic HBV hepatitis. Mean ALT and HBV-DNA levels were higher in patients with chronic HBV hepatitis ($p < 0.05$ for both; Table S1).

The frequency of allergic diseases among the groups is shown in Table S2. The frequencies of 'doctor-diagnosed asthma', 'doctor-diagnosed allergic rhinitis' and 'doctor-diagnosed eczema' were 29.4%, 7.8% and 7.8% in HBV carriers; 7.8%, 5.2% and 5.2% in patients with chronic HBV hepatitis and 12.4%, 9% and 2.8% in healthy controls, respectively. 'History of ever wheezing', 'doctor-diagnosed asthma' and 'doctor-diagnosed eczema' were more common in HBV carriers than in healthy controls ($p < 0.05$ for all parameters, odds ratios [OR]: 2.7, 2.9, 5.3 and 95% confidence intervals [CI]: 1.3–5.6, 1.3–6.4 and 1.5–19.2, respectively). Furthermore, 'history of ever wheezing' and 'doctor-diagnosed asthma' were more common in HBV carriers than in the patients with chronic HBV hepatitis ($p < 0.05$ for all parameters). Five children with asthma and two with allergic rhinitis in the HBV carrier group were followed in our paediatric allergy unit and sent to our hepatology department for HBsAg positivity.

Skin prick test results are shown in Table S3. Positive results for at least one allergen and for two or more allergens were more common in HBV carriers than in healthy controls (35.2% vs. 18%, $p < 0.05$ and 25.4% vs. 11%, $p < 0.05$, respectively) and in patients with chronic HBV hepatitis (35.2% vs. 15.7%, $p < 0.05$ and 25.4% vs. 7.8%, $p < 0.05$, respectively). Dp and Df were the common allergens among the groups. No significant difference was found between groups in terms of total IgE levels and family history of allergic diseases.

When patients with chronic HBV hepatitis (groups 1 and 2) were compared with the healthy controls 'history of ever

wheezing' and 'doctor-diagnosed eczema' were found to be significantly higher in patients than controls (28% vs. 16.7% and 10.1% vs. 2.9%, respectively; $p < 0.05$ for both).

Table S4 shows the risk factors for atopy in patients. No significant difference was found with respect to age, gender, known duration of HBsAg positivity, ALT and HBV-DNA levels in each patient group divided according to the presence or absence of atopy. However, vertical transmission was determined to be more common in patients with versus without atopy in the HBV carrier group (33.3% vs. 9%, $p < 0.05$).

DISCUSSION

In this study, we showed that the frequency of allergic diseases, asthma and rhinitis, and atopy were increased in HBV carriers compared to healthy children and patients with chronic HBV hepatitis. *Dp* and *Df* were the most common allergens among the groups and the frequency of atopy was significantly high in HBV carriers with vertical transmission.

The association of allergic diseases and atopy with CD4⁺ Th cells has been defined with Th2-type immune responses reported as responsible for the allergic diseases in genetically susceptible individuals. In contrast, Th1-type immune responses are involved in the pathogenesis of organ-specific autoimmune diseases. Balance between these two subsets of CD4⁺ Th cells directs the immune response from one pathway to the other, and causes different conditions. Environmental and genetic factors are the major contributing factors in Th1/Th2 differentiation (7–9).

HBV is a noncytopathic virus and liver damage is mainly mediated by host immune response against virus-infected liver cells. This immune response leads to the termination of infection when it is well organized or persists to a chronic disease when it is not (1). Acute self-limited HBV infection or acute exacerbations of chronic HBV infection is characterized by a strong HBV envelope/core-specific Th1-type cytokine response and polymerase-specific cytotoxic T lymphocyte reactions, which cause the termination of infection (7,14,15). In a longitudinal study it was shown that serum levels of IL-12, a cytokine essential for the Th1-type immune response, are associated with the clearance of HBV and anti-HBe seroconversion in acute hepatitis (16).

It is thought that T cell response prevalent with Th2 type contributes to viral persistence and chronicity (17,18). Contrary to this, Lee et al. (19) studied the cytokine profile of patients with chronic hepatitis and found expression of both Th2- and Th1-type cytokines in 50% of chronic hepatitis patients. Additionally, they revealed that expression of Th1-type immune response increased with severity of liver damage. Moreover, Jiang et al. (20) showed that the levels of Th1-type cytokines were positively correlated with hepatic inflammatory activity in chronic HBV infection. On the other hand it was shown that HBV surface antigen-specific Th1-type immune response is deficient in HBV carriers without any liver damage (21). All of these studies confirm that Th1-type immune response is insufficient in HBV carriers and Th1-type immune response is dominant in patients with chronic hepatitis. As a result, Th2-type immune response

may develop in HBV carriers and they may have an increased tendency to the allergic diseases and atopy. Even though we did not study the cytokine profiles of our patients, we found that prevalence of atopy, asthma and eczema were higher in HBV carriers. We also revealed that atopy was more common in HBV carriers with vertical transmission suggesting that prolonged duration of insufficient Th1-type immune response, namely, prolonged duration of Th2-type immune response, increases the risk of atopy.

The association of HBV with atopy was studied previously, but investigations were based mostly on the presence of HBsAg. Matricardi et al (22) studied the association of hay fever and asthma with markers of infection including HBV, and they found no association of asthma and hay fever with HBV seropositivity. Koh et al (23) found an inverse association of atopy with the presence of anti-HBs in young adults and they claimed that vaccination or natural immunity to HBV decreases the frequency of atopy and might be associated with strong Th1 type immune response during the acute phase of the disease. Kocabas CN (24) stated that HBV carriers have increased tendency to develop allergic diseases due to insufficient Th1 type immune response.

In this study, we found that the prevalence of 'doctor-diagnosed allergic rhinitis' and 'allergic rhinitis symptoms' was high in the control group. This may be due, in part, to our evaluating the control group in the winter period during mid-term school holiday, with parents perhaps confusing upper respiratory tract infection or flu-like symptoms with allergic rhinitis symptoms. Another limitation of our study is that we cannot exclude type 1 statistical error because of the small number of the patient group.

Many vaccination programs have been studied in HBV carriers, and the main target of these vaccinations is to increase the Th1 response proportionately with the increase in interferon- γ secretion. Synthetic oligodeoxynucleotides vaccinations that contain unmethylated CpG motifs have been shown to be effective for increasing Th1 response. Additionally, they decrease the eosinophilic infiltration and bronchial reactivity and enhance specific Th1 immune response to specific allergens (25). We believe that further studies will be held to analyse the effect of synthetic oligodeoxynucleotides vaccinations with unmethylated CpG motifs for the treatment of allergic disease and atopy in chronic HBV carriers. On the other hand, interferon and other antiviral treatments for chronic hepatitis might be evaluated on two points: effect of the presence of atopy and allergic disease on the treatment response, and effect of treatment on the frequency of atopy and allergic diseases at the end of the therapy.

In summary although our patient cohort was small, we showed that the prevalence of allergic diseases and atopy increased in HBV carriers due to immunologic response of the host, thus suggesting that these patients should be followed for the allergic diseases along with their viral reactivation.

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Supplementary material

The following supplementary material is available for this article:

Table S1 Demographic and clinical features of the patients and control group

Table S2 Frequency of allergic diseases among the groups

Table S3 Frequency of atopy among the groups

Table S4 Risk factors for atopy in patients

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