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ORIGINAL ARTICLE

Do Different Vaccination Regimens for BCG and Hepatitis B Affect the Development of Allergic Disorders in Early Childhood?

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Aim. To determine whether age at *bacilli Calmette-Guérin* (BCG) and hepatitis B vaccination has an effect on the development of atopy and allergic disorders in early childhood. **Methods.** This was a cross-sectional study of 109 children aged between 24 and 36 months with respiratory system diseases. The study population was divided into two groups according to vaccination regimens: group 1, beginning hepatitis B vaccination at birth and receiving BCG vaccine at two months of age; group 2, receiving BCG vaccine at birth and beginning hepatitis B vaccination at two months of age. Atopic status was assessed by skin-prick tests (SPTs). **Results.** There was no statistically significant difference in atopy between two groups ($p = 0.27$). However, the prevalence of recurrent wheezing was higher in group 1 (36.4%) than group 2 (16.3%) ($p = 0.04$). Logistic regression analysis identified receiving BCG vaccine at birth and beginning hepatitis B vaccination at the age of two months were protective for recurrent wheezing (odds ratio 0.5; confidence interval: 0.3–0.8; $p = 0.01$). **Conclusion.** We believe that the administration of BCG vaccine at birth and hepatitis B vaccine at two months may be protective against recurrent wheezing but doesn't prevent atopy.

Keywords atopy, BCG, hepatitis B, vaccine

INTRODUCTION

Vaccines have been implicated as a cause of the rising incidence of asthma and allergic disorders in developing countries (1, 2). Some studies have suggested that vaccines increase the risk of atopy (1–3), while others suggest that they decrease it (4–5) or are not associated with it (6, 7). The Hygiene Hypothesis postulates a relationship between infection and allergy, whereby allergic diseases are prevented by infection in early childhood. This hypothesis has been used to explain the observed increased incidence of allergic disorders in developed countries, which is attributed to the reduction of childhood infection by vaccination and improved living standards (8). This hypothesis was contrary to the previous view that infection acts as a trigger for allergy and was not widely accepted until the early 1990s, when the distinction between different types of T helper cells (Th) was discovered. Th cells play a key role in atopic disease and are broadly categorized into two subtypes based on the cytokines they produce. Th1 cells preferentially produce interleukin (IL)-2, IL-12, interferon-gamma (IFN- γ), and tumor necrosis factor- α (TNF- α) and are implicated in the development of delayed (type IV) hypersensitivity reactions in chronic granulomatous diseases, such as tuberculosis, leprosy, and sarcoidosis. Th2 cells, on the other hand, produce IL-2, IL-4, IL-5, IL-9, and IL-13 but not IFN- γ . These cytokines are important in inducing synthesis of IgE and activating eosinophils, which have a role in the pathogenesis of asthma (9). Th1 and Th2 cells are reciprocally regulated, and the IFN- γ produced in the Th1 response suppresses the Th2 response. Several stud-

ies support that pregnancy is associated with a strong skewing of the immune system away from a Th1-type and toward a Th2-type response at the maternal-fetal interface. A general Th2 skewing of the immune system during pregnancy has also been proposed (10). The postnatal maturation of the immune system, which is characterized by the development of a balanced Th1/Th2 immunity, is genetically determined and modified by the environment. The process seems to proceed at a slower rate in atopic than nonatopic infants (11).

Some viral infections may reduce the risk of atopy, and this is based on the concept of their ability to divert the immune system toward the Th1 responses. Th1 responses are important for the viral clearance of hepatitis B vaccine (HBV) and for antibody production. Koh et al. reported that the presence of anti-HBs produced by a natural HBV infection or vaccination might be inversely associated with atopy in young adults (12). De Stefano et al. found weak, significant associations between asthma and HBV (13).

In the medical literature, although there were many studies on the relationship between vaccination and atopy, we found only a few studies comparing different vaccination regimens of *bacilli Calmette-Guérin* (BCG) and HBVs in terms of atopy (14, 15). To our knowledge, this is the first study designed to investigate whether age at BCG and HBV has an effect on the development of atopy and/or allergic disorders in early childhood.

METHODS

Study Population

A total of 148 children with lower respiratory system diseases (e.g., recurrent wheezing, pneumonia, and bronchopneumonia) and aged between 24 and 36 months were admitted to the Paediatric Service of Ministry of Health Ankara Training and Research Hospital during 2003–2006.

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The children born prematurely, those with malnutrition and congenital anomalies, or those admitted to the newborn intensive care unit, twins, and children without an immunization card or parental approval were excluded. Therefore, 109 (73.6%) children were included in this cross-sectional study.

Detailed information on age at vaccination was available from the immunization cards of the children. In general, all children in Turkey possess a standardized immunization card where all vaccinations are recorded at the time they are given. The children were seen for follow-up visits at the well-infant units of the different government hospitals. All children were from similar social environments.

In all children, diphtheria/tetanus/pertussis and oral polio immunizations were administered at ages 2, 4, 6, and 18 months and measles at the age of 9 months. However, they had dual immunization plan coverage for BCG and HBVs. According to the vaccination regimens, the study population was divided into two groups as follows: Group 1 included the children vaccinated for first dose of hepatitis B at birth (within the first week of life) and BCG at two months of age, and group 2 included the children vaccinated for BCG at birth (within the first week of life) and the first dose of hepatitis B at two months of age. All children received the second hepatitis vaccination one month after the first and the third dose six months after the first.

Questionnaire

The self-administered parental questionnaire included information concerning demographic characteristics, family history of atopy, and possible risk factors, such as: breastfeeding (<6 months), cow milk consumption (>500 mL per day), low income (<\$350 for a family with two children/per month), exposure to passive smoking, and overcrowded housing (>4 family members).

Definition of Allergic Disorders

Atopic dermatitis was diagnosed from a combination of dry skin and at least three of nine typical signs (itching, erythema, red papules, vesicles, cheilitis, excoriation, lichenification, and perifollicular accentuation) in at least 3 of 26 typical anatomic sites (e.g., cheeks, infra-auricular, extensor, or flexural areas) (16). Recurrent wheezing was defined as three or more episodes of wheezing in the preceding 12 months. An episode of wheezing was defined as one or more consecutive days of wheezing preceded and followed by a healthy period of at least one week (17). To keep the reporting bias low, all children received a standardized physical examination by the same physician.

Blood Sampling and Laboratory Analysis

All of the children provided blood samples following parental approval. The samples were analyzed in one laboratory (Ankara Training and Research Hospital, Ankara, Turkey) for peripheral blood eosinophil count and serum total IgE antibodies. An ethylenediaminetetraacetic acid (EDTA) blood sample was collected for eosinophil counts by the automated hematology flow cytometer, Technicon-H*3 (Bayer, Tarrytown, New York, USA). At the same time, a venous

blood sample was separated and stored at -20°C to perform the measurements of serum total IgE concentration, using nephelometry (Immagine Immunochemistry System; Beckman Coulter, California, USA).

Skin-Prick Tests (SPTs)

Sensitivity to nine common allergens (*Dermatophagoides pteronyssinus*, mold mix, grass mix, tree pollen, cockroach antigen, cereal mix, tomatoes, cow milk, and egg protein) was assessed using standardized allergen extracts and control solutions (Stallergens S.A.-Pasteur, France) in all subjects. Allergens were applied on the volar side of the left forearm, according to the manufacturer's recommendations. Positive (histamine 10 mg/mL) and negative (diluent) controls were applied as well, and a wheal diameter ≥ 3 mm after subtraction of the negative control was defined as a positive skin reaction. The same batches of each extracts were used in the SPT. The parents of all children involved in the study gave their informed consent. The research protocol was approved by the local ethics committee.

Statistical Analysis

All data were entered in a database. Analyses were conducted using the SPSS software package, version 10.0 (SPSS Inc., Chicago, Illinois, USA). Mean values were expressed as $\pm$ standard deviation (SD) with 95% confidence intervals (CIs). An independent Student's *t*-test was used to analyze independent groups. The chi-square test was used to compare the categorical variables. The odds ratio (OR) and logistic regression analysis were done with presence of recurrent wheezing as the dependent variable and possible risk factors of interest as independent variables. Because blood eosinophil count and serum IgE concentrations follow a log-normal distribution, all subsequent analysis were performed on log-transformed scales and geometric mean values were used. A statistically significant level was accepted at a *p*-value (two tailed) equal to or less than 0.05.

RESULTS

Demographic and health characteristics of all study subjects are given in Table 1. There were no statistically significant differences between the groups with respect to their ages and gender ($p = 0.13$ and 0.58 , respectively). In group 1 (beginning HBV at birth and receiving BCG vaccine at the age of two months), 42.5% had allergic disorders, and in group 2 (receiving BCG at birth and beginning HBV at the age of two months), 30.5% had allergic disorders. As the two groups were compared for having allergic disorders, no statistically significant difference was detected between them ($p = 0.27$). However, the prevalence of recurrent wheezing was higher in group 1 (36.4%) than group 2 (16.3%) ($p = 0.04$).

To assess the independent effects of risk factors on recurrent wheezing, the possible risk factors, including age, gender, family history of allergic disease, breastfeeding, cow milk consumption, income level, passive smoking, SPT positivity, eosinophil count, total IgE level, age at vaccination for BCG, and hepatitis B, were taken into account. Multivariate analysis confirmed that receiving BCG vaccine at birth and beginning HBV at the age of two months were

TABLE 1.—Demographic and health characteristics of the study subjects.

	Group 1 n = 66	Group 2 n = 43	p-value
Age (months) (mean $\pm$ SD)	26.4 $\pm$ 2.7	25.7 $\pm$ 1.8	= 0.13*
Gender (%)			
Boy	37 (56.1)	21 (48.8)	= 0.58**
Girl	29 (43.9)	22 (51.2)	
Family history of atopy (%)			
No	55 (83.3)	34 (79.1)	= 0.75**
Yes	11 (16.7)	9 (21.9)	
Allergic disorders (%)			
No	38 (57.5)	30 (69.7)	= 0.18**
Yes	28 (42.5)	13 (30.3)	
Recurrent wheezing	24 (36.4)	7 (16.3)	= 0.04**, = 0.01***
Atopic dermatitis	4 (6.1)	6 (14.0)	
Breastfeeding (<6 months) (%)			
No	9 (13.6)	8 (19.6)	= 0.66**
Yes	57 (86.4)	35 (81.4)	
Cow milk (>500 mL/day) (%)			
No	15 (22.7)	11 (25.6)	= 0.91**
Yes	51 (77.3)	32 (74.4)	
Low income (<\$350 per month) (%)			
No	44 (66.7)	31 (72.1)	= 0.69**
Yes	22 (33.3)	12 (27.9)	
Exposure to passive smoking (%)			
No	28 (42.4)	21 (48.8)	= 0.64**
Yes	38 (57.6)	22 (51.2)	
Overcrowded housing (>4 members) (%)			
No	18 (27.3)	7 (16.3)	= 0.16**
Yes	48 (72.7)	36 (83.7)	

Group 1, hepatitis B at birth and BCG at two months of age; Group 2, BCG at birth and hepatitis B at 2 months of age.
p-value for *independent t-test, **chi-square test, ***multivariate logistic regression analysis.

protective for recurrent wheezing (OR, 0.5; CI: 0.3–0.8; $p = 0.01$).

The overall prevalence of atopy (at least one positive SPT reaction) was not significantly higher in the first group than the second group ($p = 1.00$). The geometric mean values of blood eosinophil count and serum total IgE were not different between the groups ($p = 0.32$ and 0.13 , respectively) (Table 2).

TABLE 2.—Prevalence rates of atopic sensitisation to common allergens, blood eosinophil counts, and levels of total IgE in all subjects.

	Group 1 n = 66	Group 2 n = 43	p-value
Overall prevalence of atopy (%)	14 (21.2)	9 (21.0)	= 1.00**
DP ^a	2 (3.0)	2 (4.7)	
Mold mix	3 (4.5)	2 (4.7)	
Grass mix	1 (1.6)	1 (2.3)	
Tree pollen	2 (3.0)	1 (2.3)	
Cereal mix	2 (3.0)	1 (2.3)	
Egg protein	4 (6.1)	2 (4.7)	
Eosinophil count, log ($\times$ $10^9/L$) (geometric mean $\pm$ SD)	-0.2 $\pm$ 0.5	-0.3 $\pm$ 0.4	= 0.32*
Total IgE, log (IU/mL) (geometric mean $\pm$ SD)	1.1 $\pm$ 0.8	1.3 $\pm$ 0.7	= 0.13*

Group 1, hepatitis B at birth and BCG at 2 months of age; Group 2, BCG at birth and hepatitis B at 2 months of age.

^a Dermatophagoides Pteronyssinus.

p-value for *independent t-test and **chi-square test.

DISCUSSION

This cross-sectional study revealed that age at vaccination for BCG and hepatitis B might affect the development of recurrent wheezing at 24–36 months of age. Gruber et al. investigated the association of the BCG vaccination and atopic manifestations, and they demonstrated a weak protective effect of BCG vaccination against asthma but a much stronger protective effect of non-German ethnicity against atopic manifestations among preschool children from Germany (18). Aaby et al. reported less atopy (by allergen skin-prick testing) in infants receiving BCG in Guinea-Bissau, particularly if the BCG was administered in the first week of life. They also found that when the BCG vaccine was not given until after six months of life, there was no significant decreased risk of atopy in children (19). The timing of BCG vaccination may be of central importance, because studies have indicated that a “window of opportunity” may exist for influencing Th1/Th2 balance. Newborns have an immune response that is tilted toward a Th2 response. However, infants vaccinated with BCG at birth or two months develop a Th1 response against BCG antigens (20).

In Japan, children with positive tuberculin skin-test results, induced by BCG vaccination at birth, have reduced asthma incidence and allergen sensitization. Children with a positive delayed hypersensitivity to tuberculin skin-test response had serum cytokine concentrations suggestive of a predominant Th1 response, in contrast to the Th2 profiles seen in children with a negative tuberculin skin-test result (21).

However, Alm et al. have reported that early BCG vaccination in children with atopic heredity did not affect the development of atopic diseases (22). Townley et al. studied on 1704 infants who received BCG vaccine at birth in three countries. They showed an association between negative purified protein derivate (PPD) response versus any positive PPD response and the risk of having an allergic history at the age of two years in Turkey and Thailand but not Argentina (23). In another study from Norway, 891 subjects who were BCG vaccinated at the age of 14 were investigated. When aged 20–44 years, the subjects were tested using tuberculin, and no significant relationship between a positive tuberculin reaction and atopy was observed (24). It is very difficult to compare these studies and to draw firm conclusions from them, particularly deciding whether or not BCG inhibits atopy in humans or whether it might if given very early in life. The differences between the studies reported by Shirakawa et al. (21) and others could be due to the difference in timing of BCG vaccination. Whereas the subjects in the studies by Shirakawa et al. (21) and Townley et al. (23) were immunized at birth or younger than two months, those subjects studied by other investigators were immunized as late as six months of age and later.

In contrast to BCG vaccine, there are only a few studies on allergic disorder risk after HBV or data suggesting an association between hepatitis B and allergic disorders. The hepatitis B immunization is a dead virus, and live attenuated vaccines characteristically produce a more Th1-oriented response than dead ones; it makes sense that live BCG vaccine produces a more Th1-oriented response than HBV. However, the immunologic response to the hepatitis B surface antigen used in the vaccine appears to be predominantly Th1 (25). Th1 responses are important for the viral clearance of

hepatitis B virus and also for antibody production. In a cohort study, Koh et al. reported that the presence of anti-HBs produced by a natural HBV infection or vaccination might be inversely related to atopy in young adults (12). Maher et al. studied on a total of 1778 full-term infants and concluded that childhood asthma was not significantly associated with having received HBV or age at first HBV (26). Benke et al. reported that there was no association between asthma and HBV in young adults (27). Similarly, Mullooly et al. investigated the possible associations between vaccines and incidence of wheezing in full-term infants. They also found no evidence that risk of first wheeze is associated with exposure to HBV or others and concluded that recent increases in wheezing during infancy do not appear to be related to increases in vaccinations of full-term infants (28).

In Turkey, in the past, BCG vaccine had been routinely administered to all infants at birth and HBV had been started at two months of age according to old National Health practices. After August 2003, the Ministry of Health changed the immunization regimen and offered receiving the first dose of HBV at birth because of high hepatitis B prevalence in Turkey (29) and delaying BCG vaccine at two months of age to reduce its complications (30). Despite the official recommendations, some government hospitals can prefer different vaccination regimens in our country. Therefore, we designed this study to compare two different vaccination regimens in terms of atopy and allergic disorders.

We didn't find significant differences according to atopy prevalence, eosinophil count, and IgE levels between the groups. In our study, we did not use a placebo group and it is unlikely that a large placebo group will ever be available in Turkey because of public health requirements.

CONCLUSION

In our study, similar to Townley et al.'s study (23), we didn't find significant difference between two groups in terms of atopy. This study also showed that beginning hepatitis B vaccination at two months of age may be more protective for recurrent wheezing than having the vaccine at birth. Prospective, controlled studies, which carefully take account of genetic and other variables, are needed to test the potential effects of vaccines. Further studies would be required before vaccination schedules were changed.

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