

PROFESSOR KANGMO AHN (Orcid ID : 0000-0003-0618-3947)

DR MAN YONG HAN (Orcid ID : 0000-0002-9077-5779)

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**Hepatitis B immunogenicity after a primary vaccination course associated
with childhood asthma, allergic rhinitis, and allergen sensitization**

Dong Keon Yon, MD¹

Eun Kyo Ha, MD¹

So-Yeon Lee, MD, PhD²

Woo Kyung Kim, MD, PhD³

Yong Mean Park, MD⁴

Jihyun Kim, MD, PhD^{5,6}

Kangmo Ahn, MD, PhD^{5, 6}

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Myung-Il Hahm, PhD⁷

Yoomi Chae, MD⁸

Kee-Jae Lee, PhD⁹

Ho-Jang Kwon, MD, PhD¹⁰

Man Yong Han, MD^{1*}

¹ Department of Pediatrics, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea

² Department of Pediatrics, Hallym Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea

³ Department of Pediatrics, Inje University Seoul Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea

⁴ Department of Pediatrics, Konkuk University Hospital, Konkuk University School of Medicine, Seoul, Republic of Korea

⁵ Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

⁶ Environmental Health Center for Atopic Diseases, Samsung Medical Center, Seoul, Republic of Korea

⁷ Department of Health Administration and Management, Soonchunhyang University College of Medical Science, Asan, Republic of Korea

⁸ Department of Occupational and Environmental Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

⁹ Department of Information and Statistics, Korea National Open University, Seoul, Republic of Korea

¹⁰ Department of Preventive Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

Running title: Relationship of allergic diseases with hepatitis B immunogenicity

*** Corresponding authors**

Professor Man Yong Han, MD

Department of Pediatrics CHA University School of Medicine 351 Yatap-dong, Bundang-gu, Seongnam, Gyeonggi-do, 463-712, Korea

Phone: +82-31-780-6262

Fax: +82-31-780-5239

Email: drmesh@gmail.com

Abbreviations

AD, atopic dermatitis;

anti-HBs, antibodies against the hepatitis B surface antigen;

AR, allergic rhinitis;

aOR, adjusted odds ratio;

CI, confidence interval;

ISAAC, International Study of Asthma and Allergies in Childhood;

OR, odds ratio;

SPT, skin prick test;

regulatory T cells, Treg.

Keywords

Allergy; Hepatitis B virus; Vaccination; Korea.

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TO THE EDITOR

Introduction

There have been significant advances in our understanding of the immunology of allergic diseases in recent years. Most recent studies emphasize the importance of downregulation of Th1 and Th2 responses by regulatory T cells (Tregs), which is mediated by anti-inflammatory cytokines such as IL-10, rather than an imbalance of Th1 and Th2 responses.(1, 2) Many immuno-epidemiological studies on the relationships of allergic diseases with infections or vaccines have focused on the immunological backgrounds of the study subjects.(1, 2) However, few large-scale immuno-epidemiological studies have focused on the host effect of individuals, with consideration of the presence of immune and allergic diseases. We investigated nationwide epidemiologic study on Korean children who received a 3-dose primary vaccination course against hepatitis B to assess the relationship of hepatitis B immunogenicity with the prevalence of different allergic diseases.

Methods

A nationwide cross-sectional survey was administered to 4112 first-grade students (12 years-old) who attended 40 different middle schools in the Republic of Korea. All participants were randomly selected, using a stratified two-stage cluster sampling design, between October and November of 2010.(3) We reviewed the survey responses to identify demographic factors and determine the prevalences of allergic diseases, based on criteria of the International Study of Asthma and Allergies in Childhood (ISAAC) phase III study.(3) We defined a child as having atopic dermatitis (AD) or asthma based on symptoms in the previous 12 months. Allergic rhinitis (AR) was defined by one or more positive skin prick tests (SPTs) and the presence of symptoms in the previous 12 months. Parental AD, AR and asthma required previously diagnosis by a physician. Household income was divided into

tertiles (below 2897; 2898 to 4935; and above 4836 \$US/month). We reviewed the vaccination histories of all participants.

We performed skin prick tests using the following 18 common inhalant allergens:(3) *Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, *Alternaria*, *Aspergillus fumigates*, cat dander, dog dander, cockroach, *Tyrophagus putrescentiae*, alder, birch, Japanese cedar, oak, Japanese hop, mugwort, ragweed, Bermuda grass, orchard grass, timothy. Subjects with no responses were considered as non-sensitized, and those who were sensitized (wheal diameter ≥ 3 mm) to one or more categories as sensitized. The presence of antibodies against the hepatitis B surface antigen (anti-HBs) was determined by a commercial immuno-chromatographic assay (Alere, Waltham, MA, USA). These results were classified as positive or negative, and were confirmed as recommended by the manufacturer.

The Korean primary vaccination regimen for hepatitis B consists of 3 doses, administered at month-0, month-1, and month-6, beginning at birth. Participants who had received all 3 doses of this vaccine were classified as having received the complete standard schedule, and all other children were excluded. The study protocol was approved by the Institutional Review Board of Dankook University, according to national law (DKUH IRB 2010-09-0260). Written informed consent was provided by the parents or guardians of participating children.

A *P* value below 0.05 was considered statistically significant. Data were analyzed using SPSS version 23.0 (IBM Co, Armonk, NY, USA). The multivariable analysis adjusted for the following covariates: sex, height, BMI z score, household income, and physician-diagnosed AD, AR, and asthma in parents.

Results

A total of 4112 Korean children received the surveys, and 3167 (77%) of them met the study criteria (Fig 1). The mean age was 12.9 ± 0.3 years-old, and each child had received the complete standard HBV vaccination course. Subjects were categorized as anti-HBs-negative ($n = 2200$, 69.3%) or anti-HBs-positive ($n = 976$, 30.7%). Among the 3167 participants, 390 (12.3%) had AD, 1526 (48.2%) had AR, and 245 (7.7%) had asthma. The anti-HBs positive group had significantly greater prevalences of asthma (9.7 vs. 7.0%, $p = 0.009$), AR (33.3 vs. 28.8 %, $p = 0.013$), and allergen sensitization (59.2 vs. 54.5%, $p = 0.014$) (Table I).

Figure 2 shows the unadjusted odds ratios (ORs), and the adjusted ORs (aORs) and 95% confidence intervals (CIs) for the relationship of anti-HBs positivity with allergen sensitization, asthma, AR, and AD, with adjustment for confounding by multivariable logistic regression. These results indicate significant positive associations of anti-HBs positivity with AR (aOR: 1.249, 95% CI: 1.045-1.493, $p = 0.015$), asthma (aOR: 1.451, 95% CI: 1.080-1.950, $p = 0.013$), and allergen sensitization (aOR: 1.226, 95% CI: 1.039-1.446, $p = 0.016$). However, there was no significant association between anti-HBs positivity and AD (aOR: 1.006, 95% CI: 0.745-1.268, $p = 0.834$).

Discussion

This is the first nationwide study to demonstrate that childhood asthma, AR, and allergen sensitization were significantly associated with presence of anti-HBs in 12 year-old children who had received the complete HBV vaccination course. Seroprotection, indicated as adequate anti-HBs antibody concentration at age 12, was 30.7% in our population. In agreement, previous studies also reported seroprotection rates of 20.5 to 88.2% in children younger than 18 years-old.(4, 5)

We found that the high immune response phenotype in 12 year-old children, indicated by an antibody response to hepatitis B, correlated with allergy prevalence. More specifically, our findings suggest that the immunogenicity of the vaccine was significantly associated with asthma, AR, and allergen sensitization. Moreover, our results are consistent with the explanation that this response is due to downregulation of Th1 and Th2 responses by Tregs, rather than an imbalance of Th1 and Th2. Tregs downregulate Th1 and Th2 responses through anti-inflammatory cytokines, such as IL-10, which are controlled by infectious immunology.(1, 2)

Although previous studies reported a correlation between the prevalence of allergic disease and immunologic phenotype,(1) the present study is the first nationwide study of the relationship between the post-vaccination response after 12 years and the prevalence of allergic diseases. Immunophenotype differences among these individuals may be attributed to various host effects, including heterogeneity of major histocompatibility complex proteins and individual differences in Treg responses.(2, 6)

In conclusion, immunogenicity of 12 year-old Korean children to the hepatitis B vaccine after the primary vaccination course is associated with childhood asthma, AR, and allergen sensitization. These results provide an improved understanding of the immune

mechanisms of allergic responses, and of the association between immunogenicity to vaccination and allergic diseases.

Sincerely,

Dong Keon Yon, MD¹

Eun Kyo Ha, MD¹

So-Yeon Lee, MD, PhD²

Woo Kyung Kim, MD, PhD³

Yong Mean Park, MD⁴

Jihyun Kim, MD, PhD^{5,6}

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Myung-Il Hahm, PhD⁷

Yoomi Chae, MD⁸

Kee-Jae Lee, PhD⁹

Ho-Jang Kwon, MD, PhD¹⁰

Man Yong Han, MD^{1*}

¹ Department of Pediatrics, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea

² Department of Pediatrics, Hallym Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea

³ Department of Pediatrics, Inje University Seoul Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea

⁴ Department of Pediatrics, Konkuk University Hospital, Konkuk University School of Medicine, Seoul, Republic of Korea

⁵ Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

⁶ Environmental Health Center for Atopic Diseases, Samsung Medical Center, Seoul, Republic of Korea

⁷ Department of Health Administration and Management, Soonchunhyang University College of Medical Science, Asan, Republic of Korea

⁸ Department of Occupational and Environmental Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

⁹ Department of Information and Statistics, Korea National Open University, Seoul, Republic of Korea

¹⁰ Department of Preventive Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

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Figure 1. Disposition of children enrolled in the study, and classification of study

subjects.

Figure 2. Summary estimates of the relationships between presence of anti-HBs and allergenicity (allergen sensitization, asthma, AR, and AD) in children, after adjustment for sex, height, BMI z score, household income, and physician-diagnosed AD, AR and asthma in parents by multivariable logistic regression. The points represent odds ratios and adjusted odds ratios, and the horizontal lines denote 95% confidence intervals.

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Table I. Demographic characteristics and ISAAC survey results in vaccinated children who were anti-HBs negative and anti-HBs positive (n = 3167).

	Anti-HBs negative (n = 2200)	Anti-HBs positive (n = 967)	<i>P</i> value
Gender, male, n (%)	1,083 (49.2)	476 (49.2)	0.999
BMI, z score, mean (SD)	-0.12 (1.09)	-0.17 (1.03)	0.285
Allergic disease, n (SD)			
Asthma (n=3120)*	152 (7.0)	93 (9.7)	0.009
Allergic rhinitis (n=3140)*	629 (28.8)	319 (33.3)	0.013
Atopic dermatitis (n = 3101)*	233 (10.8)	103 (10.9)	0.961
Allergen sensitization, n (%)	1198 (54.5)	572 (59.2)	0.014
Total IgE > 200 IU/mL, n (%)	712 (32.4)	350 (36.2)	0.034
Eosinophils > 4%, n (%)	482 (21.9)	244 (25.4)	0.036
Parental allergic history, n (%),(n=3029)*			
Asthma, current	79 (3.8)	27 (2.9)	0.243
Allergic rhinitis, current	675 (32.1)	319 (34.4)	0.214
Atopic dermatitis	138 (6.6)	69 (7.4)	0.377
Household income, \$US/month, n(%), (n=3098)*			0.165
< 2897	726 (33.7)	297 (31.5)	
2898-4935	908 (42.2)	390 (41.3)	
> 4836	520 (24.1)	257 (27.2)	

Anti-HBs: antibodies to hepatitis B surface antigen; BMI: body mass index; IgE: Immunoglobulin E; ISAAC: International Study of Asthma and Allergies in Childhood; SD: standard deviation.

* Some data were missing in the ISAAC survey.

Numbers in bold indicate a significant difference between the two groups ($P < 0.05$).



