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Negative IgG and IgE Hepatitis B Virus Antibody Status in Asthma: A Case Study

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Abstract

Hepatitis B virus (HBV) is a public health concern; introduction of the HBV vaccine has reduced rates of primary infection. However, some vaccinated subjects do not produce protective antibody (Ab) levels detectable by commercial assays, while others may lose detectable Abs after vaccination. Absence of HBV Ab responses after vaccination has been less studied in patients with asthma, who may be at increased risk of infection. In this case study we describe IgG-and IgE-HBV Ab levels in two patients: an asthmatic and a non-asthmatic control, pre and post HBV re-immunization. It is unknown how specific HBV IgE and B cell memory responses relate to protective immunity compared with IgG titer levels. We report that baseline HBV IgG Ab levels were negative in the asthma and non-asthma subjects, who were previously vaccinated with HBV vaccine. After re-immunization we observed that HBV IgG Ab levels in the asthma patient were positive, and then reverted back to negative; in non-asthma HBV IgG levels were positive, and then reverted back to negative. Baseline HBV IgE Ab levels were low in asthma, but were high in non-asthma. After re-immunization, HBV IgE Ab levels in asthma were detected then remained low. However, HBV IgE Ab levels remained high in non-asthma at each time point. Thus, (1) vaccination with HBV vaccine boosts IgG HBV responses, and to a lesser extent IgE responses and (2) vaccine induced measureable IgG- and IgE- HBV Ab responses are lower in asthma than non-asthma. Specific IgG- and IgE- HBV Ab responses are important factors for maintenance of sustained HBV Ab expression after HBV vaccination, and may contribute to regulation of immune responses.

Keywords: Asthma; Hepatitis B virus vaccine

Abbreviations

Ab	:	Antibodies
HBV	:	Hepatitis B Virus
Ig	:	Immunoglobulin

Introduction

Hepatitis B Virus (HBV) infection is a worldwide public health concern which remains highly prevalent [1], despite vaccine availability [1]. Introduction of the HBV vaccine has reduced primary infection rates [2], and generates protective Ab levels in healthy subjects. However, certain populations (HIV, kidney disease, diabetes) may have inadequate responses [3]. To our knowledge, few studies have evaluated these responses in atopic asthma.

Prior literature has reported associations of chronic HBV infections with Atopic Dermatitis, Asthma, Allergic Rhino conjunctivitis, asthma, and atopy [4]; less is known whether vaccination with HBV vaccine has any effect on diseases associated with altered IgE regulation (i.e. asthma). Previous studies in our laboratory reported that HBV vaccination induces specific IgG and IgE responses in asthmatic and non-asthmatic children [5], and that long-term persistence of IgE viral responses might contribute to protective immunity in certain populations [5]. However, in those studies, non-immune status after vaccination was not evaluated.

Patel et al. [6] assessed the rate of Ab response to the HBV vaccine in pediatric patients with psoriasis or Atopic Dermatitis (AD), and found a high rate of non-responders (53.8% in AD, and

38.5% in psoriasis) [7]. Excessive inflammation due to disease may contribute to increased rate of those without protective levels of HBV after vaccine [6]. Guidelines for management of patients who present without protective anti-HBV levels after the HBV vaccine are less well defined [6].

Although HBV vaccines have been effective at preventing infection, the duration of protection after vaccination with HBV vaccine is not well understood. The determinants of non-immune status are poorly defined and currently rely on Ab levels detectable by commercial assay standard cutoff levels [7] However, this cutoff level may underestimate immunity which is relevant to those who are at high risk to infection that require documented immunity (i.e. medical personnel).

This report describes a patient with atopic asthma and a non-asthmatic control, who present with absence of HBV sAg IgG Abs (after 3 dose primary vaccination series). The aim of the current study was to examine IgG and IgE vaccine-induced humoral immune responses, before and after HBV re-immunization. HBV immunity is an important issue especially in health care workers and pregnant women, due to potential exposure of non-immune persons. It is important to study specific IgG- and IgE- HBV Ab responses after HBV vaccination, because these factors are important for maintenance of sustained HBV Ab expression after HBV vaccination, and may contribute to regulation of immune responses.

Materials and Methods

Case Description

Patient Case History

Two adult health care workers who presented to an outpatient medical practice (Brooklyn, NY) for their yearly physicals, and thus Hepatitis B sAg Ab levels were checked. The subjects of this study are an atopic asthmatic adult (male, age 50 yr) and an atopic non-asthmatic adult control (male, age 23). The asthmatic patient did not receive immune-suppressants or corticosteroid treatment.

Both patients were up to date with their vaccines, but had a history of absence of HBV sAg IgG Abs after a three dose HBV vaccine series. Both patients received the recommended three doses (10 mcg/1.0 mL) of the HBV vaccine (RECOMBIVAX HB, Merck & Co., Inc., Whitehouse Station, NJ); 3 doses administered at 0, 1 and 6 months. Each dose is approximately 0.5 mL after reconstitution in sterile diluent, and is administered by subcutaneous injection. The fourth dose (re-immunization) was given when serology results were received, and patients were informed to return due to lack of Ab response. HBV vaccine titer levels were confirmed by positive anti-HBV IgG antibody levels (>0.034 Ab index, positive) (ELISA). CD19+ B cells: asthma: 17.2%, non-asthma: 10.3%. The clinical characteristics of the patients (pre-re-immunization) are shown in (Table 1).

ASTHMA	
Age, y	50
Male	Yes
Total serum IgE (IU/mL)	321 (range: 20- 100 IU/mL)
HBV sAg IgG Ab (Ab index)	0.006 (range: <0.034 Ab index, negative)
HBV sAg IgE Ab (Ab index)	0.50 (range: < 0.451 Ab index, negative)
History of asthma	Yes
History of allergic rhinitis	Yes
History of atopic dermatitis	Yes
NON-ASTHMA	
Age, y	23
Male	Yes
Total serum IgE (IU/mL)	150 (range: 20- 100 IU/mL)
HBV sAg IgG Ab (Ab index)	0.030 (range: <0.034 Ab index, negative)
HBV sAg IgE Ab (Ab index)	1.20 (range: < 0.451 Ab index, negative)
History of asthma	No
History of allergic rhinitis	Yes
History of atopic dermatitis	Yes
Abbreviation: HBV: hepatitis B virus; IgG: immunoglobulin G; IgE: immunoglobulin E	

Table 1: Participant characteristics pre-re-immunization.

Compliance with Ethics Guidelines

The protocol was approved by the SUNY Downstate Medical Center Institutional Review Board, and the procedures followed were in accordance with institutional guidelines involving human subjects. Informed consent for the publication of the case study was also obtained from the subjects.

Serology: Peripheral blood samples (5mL) were collected pre and post re-immunization (weeks 1-7, 5 month, 1 year). Total serum IgE levels were assayed at SUNY Downstate Medical Center (ELISA) (Bio Quant; San Diego, CA) and the data were expressed as IU/mL. The reference range for IgE level in healthy adult serum: 20-100 IU/mL.

Flow cytometric analysis. The antibody used in this study was Simultest (FITC/ phycoerythirn (PE)-conjugated reagents (CD3CD19) (BD Biosciences; San Jose, CA), and appropriately matched isotype control Abs (Simultest control gamma1/ gamma2a), as previously described [16]. Adult normal range (%) for CD19+ B cells: 6.3-20.0.

HBV Serum Ab detection: ELISA

IgG: Serum IgG Abs to HBV were determined by Enzyme Linked Immunosorbent Assay (ELISA) (Abnova Corporation, Taiwan; Fisher Scientific, Sprinfield, NJ), according to manufacturer's recommendation. Data are reported as Ab index (Range for HBV Ab IgG: positive: >0.034 Ab index).

IgE: The presence IgE-HBV Abs was determined by a modification of an ELISA using an IgG HBV ELISA kit (Abnova), as previously described [5]. All samples were run in duplicates. The plates were read using an automated microplate reader (Model Elx800; Bio-Tek Instruments, Winooski, VT); Optical Density (O.D.) measurements were read using a measurement filter of 450 nm, and a reference filter of 620 nm. For determination of HBV IgE, data are reported as Ab index. (Range for HBV Ab IgE: positive: >0.451 Ab index). Calculation of the cutoff value was calculated based on the negative control mean absorbance.

Results

HBV IgG Ab

Baseline HBV IgG Ab levels were negative in asthma and non-asthma (0.006, 0.030 Ab index, respectively) (Table 1), indicating either no prior exposure to HBV or lack of a specific immune response to immunization. After re-immunization, HBV IgG Ab levels in the asthma patient were detected briefly (weeks 6-7 p.i.), and then reverted back to negative (20 weeks p.i.). In the non-asthma subject, HBV IgG levels were positive (weeks 1-20), and then reverted back to negative (1 year) (Figure 1, lower panel).

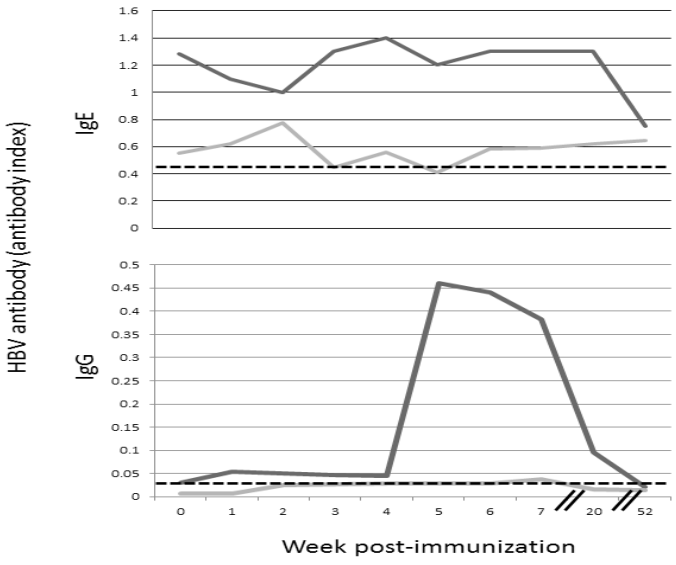

Figure 1: Differences in HBV- IgE and HBV-IgG Ab levels in asthma compared with no asthma post reimmuniztion. Top Panel: HBV-IgE Ab levels. Lower Panel: HBV-IgG Ab levels. Gray line: asthma; black line: no asthma.

HBV IgE Ab

Baseline HBV IgE Ab levels were low in asthma (0.5 Ab index), but were high in non-asthma (1.2 Ab index) (Table 1). After re-immunization, HBV IgE Ab levels in the asthma patient were detected briefly (week 2), then remained low. However, HBV IgE Ab levels remained high in the non-asthma subject at each time point (Figure 1, upper panel).

Therapeutic Intervention

No further interventions indicated. No repeat titers or follow-up indicated at this time.

Discussion

In the current study we found that in asthma, HBV IgG and IgE responses were present but low post HBV re-immunization, compared with non-asthma. It is well established that vaccine-induced Ab responses to HBV may persist for several years post vaccination [5]. However, it is possible that some people may experience weaker immune responses than others. The findings of this report indicate that negative IgG HBV Ab status and its relevance for maintaining immunity is an important area for prevention and control of HBV infection.

HBV vaccine generates protective Ab levels in healthy subjects [2], while certain populations may have inadequate responses [3]. Prior literature has demonstrated decreased seroconversion rate to HBV vaccine in HIV-infected individuals after 3 standard dose immunizations [8-9]. In addition, HIV-positive individuals who responded to the vaccine showed reduced Ab titers compared to HIV-negative controls and a decline of anti-HBV titers over time [10]. It could be, that immunodeficiency may be the major contributing factor; non-HIV-infected individuals have satisfactory immune responses (seroconversion rates between 88 and 94%) [10]. However, it should be mentioned, that the HBV vaccine is safe, and effective against HBV infection; rates of infection have declined [11].

The HBV vaccine is very immunogenic; vaccination with HBV vaccine leads to the development of IgG HBV Abs, and has the capability to protect most healthy persons against infection [12]. Liao et al reported that in HBV vaccinated children in China (5-10 years post vaccination) IgG HBV titer levels were still protective in 50% of subjects [13]. Koh, et al. demonstrated in young adults that HBV vaccination might induce T Helper (TH) 1 type immune responses, and atopy reduction [14].

However, it has been reported that 7-15% of individuals who receive HBV vaccination have no or low response to the vaccine [15], including dialysis patients with renal failure [15] and infants born form HBV-positive mothers [15]. In the present study we found in our asthma subject (who had been previously vaccinated with three doses of HBV vaccine) that after re-immunization low

levels of IgG HBV responses were briefly detected then reverted back to negative. IgE HBV levels remained constant with no association with vaccination. Ab levels were studied until one year post re-immunization so that the importance of HBV-Ab trajectory could be better understood. In contrast, in our non-asthma control, specific IgG and IgE HBV responses were higher and observed until 20 weeks post re-immunization; by one year the responses were no longer detected. It could be in asthma, pulmonary inflammation may be mediated, in part, to IgE responses, as well as other immune mechanisms. The difference observed in the humoral specificity of the response remains to be determined.

Previous studies in our laboratory reported that vaccination with the Varicella Zoster Virus (VZV) vaccine may boost IgG but not IgE-specific viral responses, and increases numbers of CD19+ B cells, in a healthy pediatric patient with negative IgG VZV Ab status (after two doses of varicella vaccine, and subsequently re-immunized) [16]. These findings are partly in line with those of our present study which demonstrated that in asthma, re-vaccination did not induce significant IgE-HBV responses, while in non-asthma IgE-HBV responses were more pronounced. It is possible that there exist fundamental differences between immune and inflammatory responses produced by asthma and non-asthma individuals before and after vaccination. IgE responses are induced by production of interleukin (IL)-4 and IL-13 by TH2 cells [17], while TH1 cell responses produce interferon-gamma, which decreases IgE production. However, these findings may imply that we don't know whether specific IgE is induced from vaccination.

In specific populations, factors associated with HBV seronegative status may include vaccine failure or waning Ab responses. The current findings have confirmed previous studies regarding protection against hepatitis B virus and primary Ab response to the vaccine [3,6]. Understanding immune responses after HBV vaccination is a challenge. It is important to continue to study individuals with low or absent protective IgG HBV Ab levels, to better understand the implications for transmission of Hepatitis B.

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Declaration of Conflicting Interest: The authors declare that there is no conflict of interest.

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