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Evaluation of the response to vaccination with hepatitis B vaccine in pediatric patients diagnosed with celiac disease

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Abstract

Background: A gap exists in the literature on celiac disease populations and the response to hepatitis B vaccination.

Objective: To identify pediatric patients with celiac disease who received the primary hepatitis B vaccination and investigate their response to vaccine.

Design/Methods: Patients underwent blood draw for hepatitis B surface antibody titers. Patients with undetectable or non-protective HBsAb titers were contacted. Study outcome measures and patient characteristics variables were summarized by means, standard deviations, medians, and ranges. A two-sample t-test was used to compare normally distributed continuous variables between responders and non-responders.

Results: In all, 58% of patients did not meet the threshold for "protective" antibody titers. The mean time between completion of hepatitis B vaccination and diagnosis of celiac disease was 8.1 years for responders versus 10.5 years for non-responders. In a multivariate analysis, time between completion of vaccine and diagnosis of celiac disease was statistically significant predictor of response with an adjusted odds ratio of 0.69 (95% confidence interval: 0.50–0.95; $p = 0.021$).

Conclusion: Our celiac disease population shows a high hepatitis B vaccine failure. The time between completion of vaccine series and diagnosis of celiac disease is an independent predictor for response.

Keywords

Celiac disease, pediatrics, vaccination

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Introduction

Despite worldwide vaccination for hepatitis B virus (HBV), an infection with this pathogen continues to be responsible for significant morbidity and mortality.[1] Infection with HBV can progress to chronic liver disease including cirrhosis and hepatocellular carcinoma. The hepatitis B vaccine was introduced in the early 1980s. In 1991, the World Health Organization recommended that all countries introduce hepatitis B vaccination into their national immunization programs.[1] In the United States, vaccination against HBV is recommended for all infants, previously unvaccinated children, and unvaccinated adults at high risk in an attempt to achieve lifelong protection against HBV infection.[1,2]

Approximately 4%–10% of healthy, immunocompetent individuals fail to mount protective levels of antibodies to recombinant hepatitis B surface antigen (HBsAg) after completing the standard HBV vaccination schedule.[1–3] Specific human leukocyte antigen (HLA) phenotype is considered the most important genetic marker for the identification of non-responders. HLA-B8, DR3, and DQ2 alleles were found to be present in the non-responders group.[2–5] Previous studies have shown a poor response to hepatitis B vaccination in adult patients with celiac disease (CD). A study in Turkey demonstrated that the hepatitis B vaccination produced protective antibody levels in only 68% of patients with CD

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compared to 100% of control subjects.[2] Researchers from Hungary[6] found that hepatitis B vaccination produced protective antibody in 95% of children and adolescents with CD who were on a gluten-free diet (GFD), compared to 51% of those who were not on a GFD. The prospective study by Park et al. showed that more than 50% of children with CD did not develop a response to intramuscular vaccination with HBV.[7] The aim of our study was to retrospectively identify children and adolescents with CD and review their vaccination status with regard to hepatitis B vaccine and determine their antibody response to hepatitis B vaccination.

Research design and methods

The University of Wisconsin–Madison Health Sciences Internal Review Board determined that this study was exempt from review. Patients with International Classification of Diseases (ICD) code 579.0 for CD were identified from the pediatric gastroenterology patients' registry at the American Family Children's Hospital. The data collection began in May 2012 and ended in April 2013. The age of the patients ranged from 2 to 18 years of age. Review of medical records was undertaken in the patients with confirmed diagnosis of CD based on serologic testing such as positive tissue transglutaminase (TTG), endomysial or deamidated gliadin peptide antibodies, and characteristic histopathology findings (partial or complete villus atrophy with crypt hyperplasia and increased intraepithelial lymphocytes). Children with positive serologies but normal endoscopies and those with negative serologies but biopsy findings suggestive of, but not conclusive for CD, were deemed ineligible. Patients with CD who had underlying immune disorders, those on immunosuppressive medications or biological therapy, and those who completed the series of vaccination within 6 months of the time of initiation of the project were also ineligible. Immunization records for hepatitis B vaccination were obtained from the Wisconsin Immunization Registry. As these patients were diagnosed with CD prior to the initiation of the study, we assumed that they were on GFD; however, we did not check the diet compliance by drawing TTG IgA antibody nor did we ask the family about diet compliance.

Eligible patients or parents/guardians of minors were informed of the project by written correspondence. Labs were obtained to determine antibody levels to HBV and HBsAg. A protective level of antibody to HBV (HBsAb) was defined as a titer > 10 mIU/mL. Subjects or parents/guardians of minor children who did not have their labs drawn within 2 weeks of the initial letter received a follow-up letter and phone call from the project coordinator. Subsequently, patients or parents/guardians of minor subjects with undetectable or non-protective HBsAb titers and negative HBsAg were contacted and given recommendations to undergo revaccination with a series of 3 hepatitis B vaccine injections.

Study outcome measures and patient characteristics variables were summarized in terms of means and standard deviations (SDs) (normally distributed quantitative variables), medians and ranges (non-normally distributed quantitative variables), or frequency and percentages (categorical variables). Histograms and normal probability plots were utilized to examine the distributions of quantitative variables. The primary outcome variable was antibody response to hepatitis B vaccine. A subject was defined as an antibody responder to HBV if he or she met the titer threshold for "protective" antibody titers. A two-sample t-test was used to compare normally distributed continuous variables between responders and non-responders. The number of comorbidities was non-normally distributed and compared between responders and non-responders using the nonparametric Wilcoxon rank-sum test. Chi-square analysis was utilized to perform the comparisons for categorical variables. Univariate and multivariate logistic regression analysis was conducted to identify independent predictors of response. Age, gender, time between completion of hepatitis B vaccination series and diagnosis of CD, existing comorbidities, number of comorbidities, and whether a subject's immunization series was administered within a 1-year time period were included as covariates in the non-parsimonious model. Predictive variables were then selected via forward selection procedure with a P-value cutoff of <0.10; a previously deleted variable was allowed to re-enter the model if its p-value was <0.10. The results of the univariate and multivariate analyses were summarized in terms of odds ratios (ORs) along with the corresponding 95% confidence intervals (CI). Statistical analyses were performed with SAS software, version 9.3 (Cary, NC). All statistical tests were two-tailed, and a p-value of less than 0.05 was defined as statistically significant.

Results

A total of 155 letters were sent from the Pediatric Gastroenterology and Hepatology clinic to identified patients or parents/guardians of minors with CD. Reminder phone calls and letters were sent to 100 patients or their parents/guardians who had not responded 2 weeks after initial contact. Among the non-responders to the letters, some had a change of address and were not able to be located, some had transferred their care to adult specialty providers, and the rest declined to have their blood drawn. In all, 54 patients (36%) responded to the letters and agreed to obtain labs. Results were available for 53 patients.

The age of the patients ranged from 2 to 10 years of age. The mean age of patients was 9.6 years (SD: 4.9). In all, 46% of the children were male (Table 1). Additional comorbidities were found in 30 (52%) of the subjects. These were type 1 diabetes (14), hypothyroidism (3), IgA deficiency (2), Down syndrome (2), autism (4), psoriasis (1), autoimmune adrenal insufficiency (1), Ehler–Danlos syndrome (1), vitiligo (1), and thyroid cancer (1). Two patients had more than one comorbidity.

Table 1. Characteristics of subjects (N = 54).

	Mean	SD
Age (years)	9.6	4.9
Time between completion of HBV vaccination and diagnosis of CD (years)	9.4	4.3
	Median	Range
Number of comorbidities	1.0	0.0–4.0
	N	%
Gender		
Female	29	54%
Male	25	46%
HBV immunization series completed within <1 year		
Yes	41	80%
No	10	20%
Number of Non-responders who completed series within <1 year	24	48%
Responder	22	42%
Non-responder	31	58%
Comorbidities		
Yes	28	52%
No	26	48%

SD: standard deviation; HBV: hepatitis B virus; CD: celiac disease.

Of the 53 patients analyzed, 31 (58%) did not have an adequate antibody response to HBV, that is, they did not meet the titer threshold for "protective" antibody titers. The mean time between completion of hepatitis B vaccination and diagnosis of CD was 8.1 years (SD: 3.8) for responders versus 10.5 years (SD: 4.4) for non-responders ($p = 0.061$) (Table 2). In the univariate analysis, time between completion of hepatitis B vaccination and diagnosis and the presence of comorbidities were marginally significant predictors for an antibody response to HBV (OR = 0.87, $p = 0.061$, and OR = 2.77, $p = 0.07$, respectively) (Table 3). In the multivariate analysis, time between completion of vaccine series and diagnosis of CD was identified as a statistically significant predictor of response to the vaccine with an OR of 0.69 (95% CI: 0.50–0.95, $p = 0.021$) after adjusting for age and the presence of comorbidities (Table 4). There were no significant differences detected between responders and non-responders in the proportion of female subjects or in the proportion of subjects who completed the vaccination series within 1 year in our study population (Table 2).

Discussion

As shown in previous studies, our patients with CD had a poor response to hepatitis B vaccination.[1–9] Over half of our tested children had either undetectable or low antibody titers to hepatitis B vaccine. A longer time period between the completion of vaccination and diagnosis of CD increased the risk for vaccination failure (Table 4). In contrast, other factors such as age, gender, and comorbidities did not correlate with vaccination failure; however, the number of patients with comorbidities in our sample was small.

Although the mechanism for hepatitis B vaccination failure in patients with CD is not clear, a few hypotheses are proposed.[2,3,5–7] It is well known that in CD, the intestinal injury is caused by interaction between specific deamidated glutamine residues of gliadin and HLA-DQ2 or DQ8 molecules. Both HBsAg protein fragments and gliadin peptides bind to HLA-DQ2 molecules; their competition can potentially result in failure to develop HBsAb.[4,8–11] Since about 90% of patients with CD carry the DQ2 HLA haplotype, this relationship can explain the high non-response rate in patients with CD. Unfortunately, the HLA haplotypes of our patients were not available at the time of data collection.

Another possible mechanism for non-response is that the concentration of antibody may have diminished over time. Low titers or the absence of antibodies may suggest lack of immunologic memory to the vaccine. As we only measured antibody titers to hepatitis B vaccine at a single time point, we cannot draw any conclusions about diminishing antibody titers over time. However, one of our patients had positive antibody titers at the time of the original diagnosis of CD and subsequently had undetectable antibody with an elevated TTG IgA antibody 1 year after diagnosis, supporting the possibility of loss of antibody level with time. Leonardi et al. revaccinated non-responders, with either intradermal or intramuscular vaccine. He found a high response rate after the first booster dose in both groups; 76.7% of patients responded to the intradermal route and 78% responded to the intramuscular route, supporting the theory of immunological memory outlasting antibody detection.[10,13] Much higher responses were documented with the third vaccine booster, with the response rate of 90% in the intradermal route and 96.4% in intramuscular route. Furthermore, those who received intradermal vaccine developed much higher antibody titers (>1000 U/L) as compared to those revaccinated intramuscularly, suggesting that the intradermal route may be a better vaccination strategy with a much more potent antibody response.[10,13]

Other studies have suggested that the response to the hepatitis B vaccine in patients with CD is dependent on compliance with a GFD.[11,12] We did not check TTG antibodies in our patients at the time the hepatitis B serology was drawn; however, we presumed that they remained on a GFD after the diagnosis was made. In 2012, Ertem et al. evaluated anti-HBs titers in patients with CD and healthy children. They demonstrated that the response to hepatitis B vaccine in children with CD who were compliant with the GFD was not different from that found in healthy controls.[2] Nemes et al. revaccinated celiac patients who had non-protective HBsAb titers with a single dose of vaccine intramuscularly. All these patients remained on a GFD at the time of revaccination. They found that 97.3% of patients seroconverted after

Table 2. Comparison between responders and non-responders.

	Responder (N = 22)		Non-responder (N = 31)		p-value
	Mean	SD	Mean	SD	
Age (years)	9.0	5.6	10.4	4.3	0.32
Time between completion of HBV vaccination and diagnosis of CD (years)	8.1	3.8	10.5	4.4	0.06
	Median	Range	Median	Range	
Number of comorbidities	0.0	0.0–3.0	1.0	0.0–4.0	0.17
	N	%	N	%	
Gender					0.59
Female	13	59%	16	52%	
Male	9	41%	15	48%	
HBV immunization series completed <1 year					0.72
Yes	16	84%	24	77%	
No	3	16%	7	23%	
Comorbidities					0.07
Yes	8	36%	19	61%	
No	14	64%	12	39%	

SD: standard deviation; HBV: hepatitis B virus; CD: celiac disease.

Table 3. Univariate analysis for predicting antibody response to HBV.

	OR (95% CI)	p-value
Age (years)	0.94 (0.84–1.06)	0.31
Time between completion of HBV vaccination and diagnosis of CD (years)	0.87 (0.75–1.01)	0.06
Number of comorbidities	0.71 (0.35–1.44)	0.34
Gender (female vs male)	1.34 (0.45–4.08)	0.59
Hepatitis B series completed <1 year (no vs yes)	0.64 (0.14–2.86)	0.56
Comorbidities (no vs yes)	2.77 (0.89–8.58)	0.07

HBV: hepatitis B virus; OR: odds ratio; CI: confidence interval; CD: celiac disease.

Table 4. Multivariate analysis for predicting antibody response to HBV.†.

	OR (95% CI)	p-value
Age (years)	1.28 (0.97–1.69)	0.081
Time between completion of HBV vaccination and diagnosis of CD (years)	0.69 (0.50–0.95)	0.021
Comorbidities (no vs yes)	3.60 (0.94–13.82)	0.062

HBV: hepatitis B virus; CI: confidence interval; CD: celiac disease.
†Parsimonious multivariate logistic regression model after variable selection via forward selection.

revaccination.[6] In contrast, Zingone et al.,[9] showed only a 68% success rate of revaccination with a complete series of three intramuscular doses of vaccine given to seronegative patients with CD, concluding that patients with CD may require a higher dose of vaccine to achieve protective antibody titers. It is important to mention that Zingone reported 68% of response in celiac patients and 91.7% response in controls about 11 years after the primary vaccination. Only 3 (5.9%) of celiac patients were on GFD at the time of primary vaccination. Despite booster vaccination, 71% of those with CD and 25% of controls still had concentrations of anti-HBs titers <10 mIU/mL.

A remaining question is whether the vaccine booster should be given intramuscularly or intradermally. The literature supports an intradermal booster as it does not rely on T-cell response but rather is mediated by dendritic cells . As suggested by Vitaliti et al.,[11,12] relying on a skin reaction at the injection site can reduce the cost of revaccination by 50%, since venous blood draws can be eliminated. In addition, intradermal injection may eliminate an unpleasant experience of blood drawing in many pediatric patients. It is not clear whether we can depend on local skin reaction as a predictor of a booster response, but data presented by Leonardi et al. in the 1990s are supportive of the intradermal route. He studied intradermal hepatitis B vaccination in 56 children with thalassemia.[14] All responders (45/56) developed delayed hypersensitivity reactions 48 h after they had received the intradermal vaccine, and a positive humoral response was always preceded by a delayed skin reaction.[14]

The limitations of our data are related to low response rate to the initial and follow-up letters, as only 36% responded to the recommended action plan. Certainly, a higher number of patients tested would have strengthened the power of analysis. It is also difficult to speculate if the existence of higher prevalence of comorbidities in our cohort altered the vaccination response. It would be interesting to study a correlation between specific HLA type, DQ2/DQ8, and antibody response to vaccine as it may vary depending on HLA type. We did not obtain TTG IgA antibody level at the time of the blood draw. This information would have been helpful to determine compliance with GFD.

In the future, we would like to study the response to revaccination with hepatitis B vaccine in patients who did not develop adequate response to primary vaccination. We will also collect TTG IgA antibody at the same time to measure compliance with GFD which may influence the response to revaccination.

In conclusion, our data confirmed previously reported low HBsAb titers in children with CD. It is unclear whether they failed to respond to the vaccine or whether the antibody titers diminished over time. If we believe that immune memory lasts despite declining antibody titers, one or two booster doses of vaccine given intradermal may be indicated for these patients. Since immunological memory persists for over 10 years after a primary course of vaccination, it may be probably practical to administer a booster of vaccine to non-responders every 10 years as Vitaliti et al.[12] recommended in their article.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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