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Inadequate seroconversion rates in celiac disease after 3 doses of hepatitis B vaccine, administered at 3, 5 and 11 months of life

Agostoni Carlo Virgimio, Boccazzi Antonio, Pontari Sara*, Bedogni Giorgio, Prampolini Luigia, Garotta Matteo, Torresani Erminio and Lunghi Giovanna
Department of Pediatrics, Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico, University of Milan, Italy

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Abstract. Celiac disease (CD) is a clinical condition potentially impairing the immune system. We tested the hypothesis that CD could hinder seroconversion following hepatitis B vaccine (HBV). We compared 81 consecutive CD patients (24 male and 57 female) with a median [interquartile range (IQR)] age of 10 (7) yr (range 2–30 yr) and 50 controls (26 male and 24 female) with a median (IQR) age 7 (7) yr (range 1–26 yr) who received a standard immunisation schedule with HBV given at 3, 5 and 11 mo of. The median (IQR) interval from the last dose of HBV was higher in CD patients as compared to controls [10 (7), range 2–29 yr vs. 6 (7), range 1–26 yr; $P < 0.0001$]. The median (IQR) age of gluten introduction was comparable in the two groups [6 (1), range 4–12 mo vs. 6(1), range 5–11 mo]. The median (IQR) duration of gluten intake in the CD group was 3.5 (4.8) yr (range 0.2–12.3 yr). 33 of 81 (40%) CD patients did not seroconvert (anti-HBs $<$ 10 IU/mL), compared with 10 of 50 (20%) controls ($P < 0.05$). The odds ratio of a protective anti-HBs titer in CD patients vs. controls was 0.36 (95% CI, 0.16–0.83, $P < 0.0001$), and was not associated with gender, interval from the last administration of HBV, or duration of pre-diagnosis gluten intake in CD patients. Our results are consistent with previous observations that CD patients are less likely to be protected by HBV, which may have important public health implications.

Keywords: Celiac disease, HBV vaccine, seroconversion, immune network

1. Introduction

Celiac disease (CD) is an immune-mediated enteropathy, caused by a permanent gluten allergy in genetically predisposed subjects [1]. The hereditary predisposition is essential and is expressed in specific class II antigens of the major histocompatibility complex homozygotes alleles DQ2 and HLA DQ8 [2]. HLA DQ2 appears as dominant in 90–95% of the CD patients, often carrying a combination of HLA DQA1*0501 and HLA DQB1*0201; the minority of patients expresses HLA DQA1*0301 and HLA DQB1*0302 (encode by HLA DQ8) [3]. Currently the diagnosis of CD includes a clinical, serologic and bioptic approach. HLA genetic study has only a limited role in diagnosis, because the presence of DQ2 or DQ8 indicates only a predisposition to develop CD [1]. Three doses of hepatitis B vaccine (HBV) induces a protective response in 95% of the pediatric subjects but specific pediatric populations do not respond well to HBV (e.g. patients with chronic renal insufficiency or cirrhosis, patients under dialysis or HIV positive children) [4–6]. We investi-

*Correspondence: Dr. Pontari Sara Laura, Department of Pediatrics, via Commenda 9 20122 Milan, Italy. Tel.: +39 0255032452; Fax: +39 0276113101 or +39 0250320226; E-mail: saralaura.pontari@virgilio.it.

gated whether CD might be another condition that impairs the response to HBV. This is of relevance in Italy where the estimated prevalence of CD in children is 0.6–1.0%. Moreover, this figure may underestimate the true prevalence because atypical manifestations of CD in childhood may not be diagnosed until adulthood [7]. CD patients might therefore constitute an important cohort from a public health perspective that are susceptible to hepatitis B, and complications such as cirrhosis and hepatocarcinoma.

2. Materials and methods

In this observational study we studied seroconversion in CD children and a control group following HBV (administered in three doses intramuscularly at 3,5 and 11 mo of life, according to the national calendar). The impact of CD on patients' ability to mount an immune response correlated with time since last HBV dose and with compliance with gluten-free diet. Anti- hepatitis B surface antigen (anti-HBs) antibody titers in CD patients were compared with those of controls. Parents gave signed consent for deceiving of versus blood. No approval by the IRB was requested for this retrospective observational study.

Children who did not receive their vaccinations within 30 days of the scheduled time, children with other autoimmune diseases and/or receiving immune-modulating therapies, and those with oncological diseases, immunodeficiency or documented previous HBV infection were excluded from the study.

Diagnosis of CD was based on standard serologic (anti gliadin-IgA/IgG antibody, tissue transglutaminases IgA antibody and anti-endomysial IgA antibody) and histological criteria (microvillous atrophy, hyperplasia of the crypts and infiltrated intra epithelial lymphocytes). Information about the age of introduction of gluten (before the diagnosis of CD), the age of the diagnosis and the compliance to a gluten free diet was obtained.

2.1. Methods

Anti-HBs antibody titers were measured using the Architect Ausab assay (Abbott Laboratories) [4]. Patients and controls with antibody titers less than 10 mUI/mL were defined "non responders", those with values of 10 to 100 mUI/mL were deemed "low responders", and those with titers of greater than 100 mUI/mL were considered "high responders" [8].

2.2. Statistical analysis

Statistical analysis was performed using Stata 11.0 software. Differences in continuous variables between groups were evaluated using the Mann-Whitney test, and in categorical variables using the Fisher test. Logistic regression was used to determine the odds of a protective antibody titer in CD patients compared with controls. This univariate analysis was followed by a multivariate analysis to evaluate the possible effect of gender and of the time since last vaccination. Logistic regression was also used to evaluate the association between a protective antibody titer and duration of gluten intake in CD patients.

3. Results

131 individuals were enrolled in the study, comprising 81 patients with CD and 50 controls. Their demographic characteristics are shown in Table 1. Four of our CD patients had HLA genomic typing: 2 were DQ2 positive and 2 were DQ8 positive. Three CD patients had other autoimmune disorders: 2 had atopic dermatitis and 1 had type 1 diabetes mellitus.

The median time elapsed since the last booster dose of HBV was higher in CD patients than in controls (10 years versus 6 years: Table 2). The median ages of introduction of gluten was comparable in cases and controls, whilst the median duration of gluten consumption in CD patients was 3.5 yr (Table 2). 40% of CD patients failed to seroconvert, compared with 20% of controls ($P < 0.05$) (Table 2).

The OR of a protective anti-HBs titer in CD patients compared with controls was 0.36 (95% CI 0.16–0.83, $P < 0.0001$), and this value was unaffected by gender or time elapsed since last booster dose (Table 3). The likelihood of a protective response to HBV was not related to duration of gluten consumption (Table 3).

4. Discussion

Our study indicates that patients with CD have an impaired response to HBV, leaving this population less protected population against hepatitis B. This finding may be explained by a defect of the immune response, such as abnormal antigenic presentation, or suppression of the Th type 2 mediated response essential for the production of anti HBsAg antibodies. Alper et al. [9] have shown that the response to HBV is relat-

Table 1
Patient demographic characteristics

	Celiac Disease ($n = 81$)	Controls ($n = 50$)
Median age (interquartile range) at enrolment in the study	10 (7) yr (range 2–30 yr)	7 (7) yr (range 1–26 yr)
Gender		
Male	24	26
Female	57	24
Ethnicity Caucasian	81	50

Table 2
Seroconversion rates in celiac disease patients and controls, and confounding variables

	Celiac disease ($n = 81$)	Controls ($n = 50$)
Titre $<$ 10 mUI/mL	33 (40%)	10 (20%)
Median time elapsed (interquartile range) since last booster dose	10 (7) yr (range 2–29 yr)	6 (7) yr (range 1–26 yr)
Median age (interquartile range) at gluten introduction	6 (1) mo (range 4–12 mo)	6 (1) mo (range 5–11 mo)
Median duration (interquartile range) of gluten consumption duration in celiac patients (before diagnosis)	3.5 (4.8) yr	

Table 3
Univariable and multivariable logistic regression

	All patients (Celiacs + Controls)	All patients (Celiacs + Controls)	Celiacs	Celiacs
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Celiac disease (Yes vs. No)	0.36* (0.16, 0.83)	0.36* (0.15, 0.88)	–	–
Male (Yes vs. No)	–	1.19 (0.53, 2.66)	–	1.01 (0.37, 2.73)
Time elapsed since last booster dose (years)	–	1.01 (0.94, 0.08)	–	1.04 (0.95, 1.13)
Duration of gluten intake (years)	–	–	1.00 (0.86, 1.15)	0.99 (0.85, 0.14)
Total	131	131	81	81

OR: Odds ratio, CI: Confidence interval, $^*P < 0.05$.

ed to the major histocompatibility complex. It is also known that subjects unable to respond effectively to the vaccine express homozygotes alleles HLA-B8, DR3 and DQ2 [10–12]. HLA DQ2 seems to constitute the pathogenetic link between CD and the poor immunity provided by this vaccination, since such alleles are expressed in 95% of CD patients [13].

Our results are comparable to those of Leonardi et al. [5] who demonstrated that 50% of CD patients, but only 11.6% of controls, had anti-HBs titers $<$ 10 mIU/mL ($P < 0.0001$). Fifteen of their patients were HLA typed: 13 were HLA DQ2 positive and 2 were HLA DQ8 positive, providing further evidence for link between HLA type and lack of the response to HBV [5]. There is no evidence that HBV is harmful in CD patients.- Belloni et al. [14] undertook autoimmune screening of 210 children after administration of HBV: only 16 of them were found to express auto antibodies, which was not statistically different to a control group of 109 unvaccinated children [14]. Co-existence of CD with other autoimmune disorders may further increase the likelihood of non-response to HBV. All three of the patients with other autoimmune conditions in our study had an inadequate response. Ahishali et al. [15] also found that CD patients with co-existing autoimmune diseases responded poorly to HBV. Park et al. [16] did not find that HLA DQ2 expression impaired the immune response to other vaccines given in infancy [16]. 14 of 26 CD patients and 2 of 18 controls had low anti-HBs titers following HBV, but all showed protective antibody titers following measles vaccination. Only 1 CD patient did not respond after receiving tetanus toxoid, vaccination, and the proportions of CD patients and controls who responded to *Haemophilus influenzae* type b vaccine were comparable [16].

It is important to consider the possibility of bias in our results due to the expected decline in anti-HBs titers over time in any vaccinated persons [5]. Prospective long term studies in normal children have highlighted that the protective antibodies against HBV decrease 48–64% after about 10–15 yr [17]. It is still unclear whether there is a connection between the non-adherence to a gluten-free diet and an inadequate response to HBV. All the CD patients in our study were reported to be fully compliant with a gluten-free diet, whilst we found no evidence of a relationship between response to HBV

and duration of gluten intake pre-diagnosis. By contrast, Leonardi et al. [5] found that early diagnosis of CD (before the 18 mo of age) did increase the chance of responding to HBV.

5. Conclusion

Our results accord with previous reports of a poor response to HBV in CD patients, which may be of public health importance. Specific guidelines are required to direct the immunization and follow-up by serological testing of this group of children [18].

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