Hepatitis B virus vaccination and revaccination response in children diagnosed with coeliac disease : a multicentre prospective study

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Abstract

***Aim* : This study evaluates hepatitis B virus (HBV) vaccination response in children with celiac disease (CD). Response in initial non-responders after a single booster vaccination as well as factors influencing HBV vaccination response were evaluated.**

***Methodology* : Anti-hepatitis B surface antibodies (a-HBsAB) were checked in all children with CD and a documented complete HBV vaccination. An a-HBsAB <10 U/L was considered as non-response. A single intramuscular HBV-vaccine booster was advised to all non-responders. Response was checked at the next appointment.**

***Results* : 133 children with CD were included, median age of 7.3 years (range 1.7-17.3) and 46 (35%) were male. The age at CD diagnosis was 6.0 years (range 1.1-15.7). HBV non-response was documented in 55% (n=73/133). No other factors were influencing the response. A booster was documented in 34/73 (47 %) initial non-responders (3 refused (4%), 36 (49%) had no follow up). Response after booster vaccination resulted in immunity in 22/34 (65%) and persisting non-response in 12/34 (35%). A single booster is able to reduce non-response from 55% (73/133) to 23% (22/94).**

***Conclusion* : A significantly lower immune response following HBV vaccination in children with CD was confirmed. A single intramuscular booster vaccination is able to induce a serologic response in two thirds of the initial non-responders. Control of HBV vaccination response has to become part of the follow-up in CD patients.** (Acta gastroenterol. belg., **2019**, 82, **27-30**).

Key words : celiac disease, hepatitis B, children, intradermal, vaccination

Introduction

Celiac disease (CD) is an immune mediated disorder triggered by gluten intake in persons with genetic predisposition. It is characterized by a combination of gluten-dependent symptoms, celiac specific antibodies e.g. anti-tissue-transglutaminase antibodies (a-TTG AB), human leukocyte antigen (HLA) (HLA-DQ2 and HLA-DQ8 haplotypes) and enteropathy (1). Treatment consists of a lifelong strict gluten free diet. Coeliac disease has an estimated prevalence of 1%, with a regional dependent variation between 0.3-2.4% (2).

Hepatitis B virus (HBV) infection is a major global health problem causing acute and chronic liver diseases, cirrhosis and hepatocellular carcinoma. Since the implementation of vaccination in the early eighties and the recommendation of the World Health Organization (WHO) in 1991, the incidence of HBV infection in Western countries diminished remarkably (3). HBV vaccination is part of the Belgian vaccination schedule since 1999 and is currently administered as a hexavalent vaccine at the age of 2, 3, 4 and 15 months (4). The immunization coverage in Belgium is high (93%) due to a free vaccination program (5). According to the international standards, an anti-hepatitis B surface antibody (a-HBsAB) titer of $\geq$ 10 IU/L is considered protective. HBV vaccination response in CD patients has been reported to be lower (30-50%) compared to the general population (90-96%) (6,7). HBV vaccination non-response is mainly associated with the genetic haplotypes HLA-DQ2 and -DQ8 (8). Patients with CD have HLA-DQ2 and -DQ8 haplotypes by definition and are therefore prone to an insufficient response to HBV vaccination (7, 8). Compliance to the gluten free diet could also play an additional role in the immune response after HBV vaccination (9-11). It is hypothesized that Gliadin peptides as well as HBsAg protein compete in HLA-DQ2 binding. As a result T-lymphocyte proliferation and antibody production might be impaired in the presence of gluten in CD patients (9-11).This study aimed to evaluate the HBV response of Flemish paediatric CD patients and to correlate the response to clinical parameters such as gender, CD presentation and activity as well as to evaluate the response to a single intramuscular booster vaccination.

Methodology

All patients consulting at the department of pediatric gastroenterology at the university hospitals in Ghent and Antwerp and the general hospital AZ Sint-Jan in Bruges (Belgium) between September 2014 and February 2017 with known or newly diagnosed CD were asked to participate. At the time of their annual follow-up, a-HBsAB was measured. The vaccination schedule was checked and only patients with a complete standard vaccination (vaccination at the age of 2, 3, 4 and 15 months) were included.

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Table 1. — **Clinical and laboratorial data reported as median and quartiles or number and percentage of the group, at the time of diagnosis and inclusion in the study. Comparison between the groups with and without HBV immunization. Abbreviations HBV : hepatitis B virus, GI : gastrointestinal complaints, FTT : failure to thrive, a-TTG : anti-tissue transglutaminase.**

			All patients (n=133)	HBV immune (n=60)	HBV not immune (n=73)
Diagnosis of CD	**Median age (y)**		6.0 (1.1; 15.7)	5.8 (1.1; 15.7)	7.1 (3.0; 12.8)
	Symptoms GI-complaints Asymptomatic FTT Fatigue Anaemia		 90 (68%) 7 (5%) 43 (32%) 14 (11%) 4 (3%)	 40 (68%) 3 (5%) 17 (29%) 6 (10%) 1 (2%)	 50 (68%) 4 (5%) 26 (35%) 8 (11%) 3 (4%)
	Weight z-score		-1.2 (-4.5; 1.7)	-0.9 (-4.2; 1.7)	-0.9 (-4.5; 1.6)
	Length z-score		-0.8 (-4.2; 3.2)	-0.8 (-3.9; 3.2)	-1.0 (-4.2; 2.5)
	a-TTG IgA		200 (0; 2675)	128 (3; 2464)	200 (0; 2675)
	Marsh type (n=126) Type 1 Type 2 Type 3		 8 (6%) 5 (4%) 120 (90%)	 5 (9%) 2 (3%) 53 (88%)	 3 (4%) 3 (4%) 67 (92%)
At study inclusion	**Median year (y)**		7.3 (1.7-17.3)	8.0 (4.0;11.0)	8.0 (5.0-15.2)
	Boys/ Girls		46(35%)/87(65%)	23(38%)/37(61%)	23(31%)/50(69%)
	a - T T G (n=129)	**Median**	5 (0; 392)	4 (0; 200)	4 (0; 392)
		<7 U/ml	87 (65%)	36 (66%)	51 (69%)
	Weight z-score		-1 (-4.1; 2.3)	-0.6 (-1.4; 2.3)	-0.4 (-3; 1.6)
	Length z-score		-0.7 (-4; 3.5)	-0.5 (-4; 3)	-0.54 (-1.42;0.65)
	Duration diet (year)		1.1 (0-13.2)	2.1 (0-12.9)	2.5 (0-13.2)

Diagnosis of CD was based on the international criteria (clinical symptoms, serological markers (a-TTG AB) and small intestinal biopsies) (1). Biopsy specimens were evaluated according to the modified Marsh criteria (12).

The age at CD diagnosis, serology at diagnosis, histology and presenting symptoms as well as therapy compliance to the diet at the time of inclusion was extracted from the patient files. Patients were considered as in remission if no mistakes were found during dietary history and the a-TTG IgA AB titer was negative (<7 U/mL) at the time of inclusion.

All patients with a-HBsAB titer <10 IU/l were advised to get a single intramuscular (IM) age appropriate HBV booster vaccination containing 10-20 µg HBs antigen eventually in combination with deactivated hepatitis A virus. At the next scheduled blood analysis the a-HBsAB response was measured.

Statistical analyses were carried out using SPSS 24. Descriptive results of the study population are reported as median and range. Statistical analysis of differences between study groups, were analyzed with Wilcoxon rank test and categorical variables with Chi-square test. A two sided test was used, a p-value <0.05 was considered statistically significant.

The study was approved by the Ethical Committee of Ghent University (EC/2015/0875).

Results

A total of 172 children with CD were available for inclusion. Thirty-nine patients were excluded due to transition to adult care (n=14), incomplete standard vaccination schedule (n=8) and loss of follow up (n=17). A total of 133 CD children were included, 46 (35%) boys and 87 (65%) girls.

The clinical and laboratory results at diagnosis and inclusion are summarized in Table 1. The median age at diagnosis was 5.1 years (range 1.7-17.3). CD presenting symptoms were abdominal complaints such as pain, diarrhoea, constipation in 68% (n= 90), weight or height ≤ -2 standard deviation (sd) in 32% (n=43), fatigue in 11% (n=14) or predisposing factors such as diabetes mellitus type I, Down syndrome and Turner syndrome in 5% (n=7). At the time of CD diagnosis, 97% (129/133) of the children had already completed the HBV standard vaccination.

At the start of the study, the median age was 7.3 years (range 1.7-17.3). Patients received a gluten free diet for 1.1 year (0-13.2). Complete disease control measured as a-TTG IgA AB < 7 U/ml, was present in 65% (87/133). Patients (n= 46) with positive a-TTG IgA AB (median titer 20 (7.7-392) were treated with a gluten free diet for 0.3 years (0 - 3.8). Only 45% (60/133) of the CD patients had a-HBsAB ≥ 10 IU/L. There was no difference in HBV immunity according to age at CD diagnosis (p=0.84), age at study inclusion (p=0.73), gender (p=0.84) or presence of a-TTG IgA AB (n=46) (p=0.77).

The patients without HBV immunity were advised to get a single IM HBV booster vaccination. This was documented in 34/73 (47 %) patients (3 refused (4%) and 36 (49%) had no follow up). An a-HBsAB titer of > 10 IU/L weas obtained in 22/34 (65%) patients. Of the 12 patients, non-responders to one IM booster vaccination, 4 repeated a complete vaccination schedule

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(booster at 0-2-6 months), with 2 (50%) responding. No data are available from the remaining 8 non-responders after a single booster 4 had transitioned into adult care, 2 were lost from follow-up and 2 refused the complete vaccination scheme. Keeping in mind the absence of data for 39 patients, total immunization rate increased from 45% (60/133) to minimally 61% (82/133) after a single intramuscular booster.

Discussion

Hepatitis B infection causing liver cirrhosis and liver cancer is a major global health problem affecting a still growing part of the world population (13). The WHO advises HBV vaccination as a key tool in the prevention of hepatitis B infection. Acquiring a-HBsAB levels ≥ 10 IU/L after vaccination is defined as vaccination response despite the fact that immunity following vaccination consists of a combination of a-HBsAB and cell-mediated memory (14). Population studies revealed 4-10% non-responders, based on a-HBsAB levels, after a complete vaccination schedule (6,7). Different non-genetic factors including age at vaccination, smoking, obesity, drug abuse and immunosuppression were described to be associated with weak or non-response (15). A physiologic decline in a-HBsABs was noticed in individuals as young as 30 years (16). Walker was the first to describe in 1981the association between HBV vaccination immune response and HLA types (17). This was confirmed by Desombere et al. DQB1*0201 and DQB1*020 were more frequently seen in persons with weak or non-response and homozygosity for these HLA haplotypes was associated to increased non-response (1,7,8). HLA molecules present intra- or extracellular antigens to the immune system inducing cell proliferation, differentiation and antibody production. In the healthy Caucasian North-American and European populations, the prevalence of HLA-DQ2 is 30-40% (7).

HLA-DQ2 serotype is also frequently associated with auto-immune diseases such as diabetes mellitus type I, Hashimoto's disease and CD (18). Of the CD patients 90%-95% carry HLA-DQ2 and 5-10% HLA-DQ 8 (19). Presentation of specific deaminated glutamine containing residues of gliadin by these HLA haplotypes, induce intestinal T-lymphocyte proliferation and a-TTG AB production. Subsequent T-helper1 cell activation and T-helper2 cell suppression in the lamina propria leads to intestinal mucosal damage (9, 20, 21).

The common genetic predisposition of HBV non-response and CD makes these patients prone to non- or weak response to standard HBV vaccination. Results of this study confirmed that children with CD in Belgium have a significant lower immunization rate after HBV vaccination than the rate in the general paediatric population (6, 7). The Belgian CD immunization response (45%) is comparable to what has been reported in the literature, namely 35-50% (8-11). The absence of gender difference confirms the results of Zingone et al. (7). Ertekin et al. however, did observe a significant response difference according to gender (11).

Lower immunization responses were observed in young adult CD patients aged 25-30 years (with correct vaccination as infants). Our study could not confirm a relation with age but no adult patients were included. The increase in non-immune young adults could be the results of the long interval between vaccination and measurement of a-HBsAB (7).

The inadequate immunization response in CD patients seems to be limited to HBV vaccination. Park et al. investigated the response to several childhood vaccines (tetanus, rubella, *Haemofilius influenza* and HBV) in individuals with and without CD. They concluded that only the response to HBV vaccination was impaired, with failure in 54% of CD patients versus 11% of control group (22).

Based on the competition of Gliadin peptides and HBsAg protein for HLA-DQ2 binding and immune system stimulation, there exists an hypothesis that vaccination in absence of a gluten free diet has poorer response rates (9-11). This study was not able to demonstrate an association between non-response and CD remission as only 46 (34%) patients still had positive a-TTG AB. However, Leonardi et al. (2015) compared the response of children with diabetes mellitus type I, with CD or with a combination of both, before the start of gluten-free diet. The percentage of non-responders was respectively 38.2%, 50% and 53.3%. Since these diseases have a similar genetic HLA background, increased non-response in case of CD was attributed to a supplementary effect of gluten intake (23). This assumption was confirmed in 2 studies comparing compliant and non-compliant CD patients (based on a-TTG IgA AB positivity) . The immunization was better in the compliant patients (10,11). On the other hand Zingone et al. did not find an association between gluten intake at the time of vaccination and HBV immune response (7). Until now, the influence of gluten intake on the HBV immunization remains unclear.

In case of non-response, a booster vaccination is recommended but there is discussion whether a single booster or a complete schedule is needed and whether IM or intradermal (ID) administration should be chosen. Leonardi et al. vaccinated children with non-response after completion of basic schedule for HBV. A single dose immunized 77.5% and after 3 doses 93.2%, where the latter reached a similar immunization rate as the control population (24). Nemes et al. (2008) described response in 97% after complete revaccination in CD children with initial non-response and good compliance to the diet (9). This study also revealed response after one booster in 61% of initial non-responders.

Furthermore, in an attempt to improve immunity after initial non-response, IM and ID administrations have been compared. Sangare et al. described a 14% higher seroconversion rate in adults with IM administration. This difference between IM and ID HBV vaccination

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was very variable in children (respectively 94-100% following IM, 41-98% following ID vaccination) (25). Leonardi et al. (2012) reported comparable response rates after single (76.7% ID vs 78.6% IM) and after 3 injections (90.0% ID vs 96.4% IM). A very high a-HBsAB titer (>1000 IU/L) was observed in 40% after ID injection and only in 7% after IM vaccination (24). Future studies are needed to further evaluate the response differences between the different administration routes as well as the evaluation of the ideal dose. Cost/benefit ratio could also be taken into account as probably a lower ID dose will be needed and visualization of the response by development of a papule might make the measurement HBs AB titers unnecessary (26, 27). Finally, questions concerning the need for booster vaccination are raised as the level of a-HbsAB's often become negative years after hepatitis B vaccination, yet protection appears to be solid and long-lasting (28).

A current pragmatic way to tackle non-response in CD patients could be a single IM booster followed by measurement of a-HBsAB 1 month after vaccination. However, persistent non-responders should be advised to go for a complete revaccination schedule which has been shown to induce immunity in a considerable number of this group.

Conclusion

Non-response to initial HBV vaccination is observed in 55% of patients diagnosed with celiac disease. A single IM booster vaccination increases the a-HBsAB levels in 47% of initial non-responders. Complete vaccination will still induce a-HBsAB in 2/4 patients. Monitoring a-HBsAB levels and booster vaccination should be included in the follow up of CD patients.

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