

Response of Hepatitis B Vaccine in Children with Celiac Disease – An Experience at Ayub Teaching Hospital, Abbottabad Pakistan

Bibi Aliaa¹, Syed Sajid Hussain Shah²

¹Assistant Professor, Department of Pediatrics, Lady Reading Hospital Peshawar, Khyber Pakhtunkhwa, Pakistan

²Assistant Professor, Department of Pediatrics, Ayub Medical College Abbottabad, Khyber Pakhtunkhwa, Pakistan

ABSTRACT

Background: Celiac Disease (CD), characterized by chronic small intestinal inflammation, is an immune-mediated disorder, with a strong family history and association with DQ2 HLA haplotype. It has been postulated that children with CD show less response to hepatitis B vaccine due to overexpression of HLA-DQ2 haplotype. This study was done to determine the response of hepatitis B vaccine in children with CD in our tertiary care setting in the Hazara region of eastern Khyber Pakhtunkhwa, Pakistan.

Material and Methods: This cross-sectional study was conducted in the Pediatrics outpatient department (OPD) of Ayub Teaching Hospital, Abbottabad Pakistan from April 2018 till March 2020. Children with CD (n=38) aged 1-14 years with completed HBV vaccination, anti-tissue transglutaminase IgA antibody (tTG-IgA) >150 IU/ml and/or typical histological findings of CD on small-bowel biopsy, were included in the study. Hepatitis B surface antibody (HbsAb) titer of ≥10 mIU/ml was taken as antibody positive, while HbsAb levels < 10 mIU/ml were considered as vaccine non-responsive. Data was analyzed using SPSS version 20.0. Chi square test was applied for comparison with *P*-value < .05 taken as significant.

Results: Out of 38 diagnosed cases of CD, 15 (39.5%) were males and 23 (60.5%) were females. Mean age of children was 8.32±3.26 years with an age range of 3-14 years. HbsAb levels ranged from 0.10 to 62.7 mIU/ml with a mean of 11.2±17.42 mIU/ml. HbsAb levels were less than 10.0 IU/ml in 73.7% of children with CD. Small intestinal biopsy was performed in 11 (28.9%) patients. There was a significant relationship between anti tTG-IgA levels and histopathology findings with *P*-value of .001.

Conclusions: In children having celiac disease, there was low rate of protective antibody response to hepatitis B vaccine.

Key words: Antibody response, Celiac disease, Hepatitis B vaccine, HbsAb levels.

Authors' Contribution:

¹⁻² Conception; Literature research; manuscript design and drafting; Critical analysis and manuscript review; Data analysis; Manuscript Editing.

Correspondence:

Syed Sajid Hussain Shah
Email: syed_sajid20@yahoo.com

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Introduction

Celiac disease (CD) is an immune mediated-disorder with a strong genetic predisposition. It is characterized by chronic small intestinal inflammation induced by ingestion of gluten moiety in the diet. Worldwide the estimated prevalence of CD in children is about 1%.¹ In 2010, 2.2 million children under five years of age were diagnosed with celiac disease. It has an immunological basis as evidenced by a strong family history and association with the DQ2 HLA haplotype. Individuals lacking the DQ2 haplotype are generally positive for DQ8.²⁻⁴

Hepatitis B virus (HBV) vaccine was introduced in the early 1980s for use in individuals at high risk for acquiring HBV infection. In Pakistan, it is currently administered to all infants as part of the EPI (Expanded Programme on Immunization) program. It is also administered to previously unvaccinated adults at high-risk, in an attempt to achieve universal protection against HBV infection. A course of three doses of hepatitis B vaccine can be administered in a variety of schedules: such as at birth, 1- and 6-months schedule, the 6-, 10- and 14-weeks doses and the 2-, 4- and 6-months schedule. All schedules induce protective levels of antibody to hepatitis B surface antigen (HbsAg) in majority of healthy infants and children.⁵ About 90% of adult population respond to HBV vaccination.⁶ Non-responders are often found to carry specific human leukocyte antigen (HLA) haplotype, including DR7, DR3, and DQ2.⁷

Since the HLA-DQ2 haplotype is over-represented in celiac population, it seems reasonable to hypothesize that patients with Celiac Disease are less able to respond to HBV vaccine than the general population, whose frequency of HLA haplotype B8, DR3, and DQ2 are much lower. It has been postulated that this genetic profile may play a crucial

role in predisposing celiac patients to a lower grade of immunization to hepatitis B vaccine.⁸

CD is not an uncommon disease. There is scarcity of data regarding exact prevalence of CD and response of children with CD to hepatitis B vaccination.⁹ The problem of chronic HBV infection and its associated complications like liver carcinoma remains a major public health problem. Children with CD who are non-responsive to HBV vaccination could be considered as a large reservoir of HBV-susceptible individuals who will persist as healthy carriers, leading to spread of the disease in healthy subjects. This study was therefore carried out to determine the response of hepatitis B vaccine in children with CD presenting in the outpatient department (OPD) of Pediatrics at Ayub Teaching Hospital, Abbottabad, Pakistan.

Material and Methods

This cross-sectional study was conducted in the Pediatrics OPD of Ayub Teaching Hospital, Abbottabad in Hazara Division, KPK, Pakistan from April, 2018 till March, 2020. Approval was sought from the Ethics Committee of Ayub Medical Institutions, Abbottabad Pakistan. Informed consent was taken from parents prior to the conduct of research. Sample size (n=27) was calculated with OpenEpi sample size calculator for cross-sectional studies, taking prevalence of CD in children as 1%¹ and confidence interval of 95%. A total of 38 patients were included in the study using purposive sampling technique. The study population included both new and old cases of celiac disease diagnosed during the study period. Children aged 1 to 14 years, diagnosed with CD on the basis of a thorough history were included. Laboratory diagnosis of CD was done on standard clinical criteria including abnormal serological marker, anti-tissue transglutaminase IgA

antibody (tTG-IgA) >150 IU/ml and/or small-bowel biopsy histological findings such as villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes. Biopsy was not done in patients with anti tTG-IgA level >150 IU/ml. Other inclusion criterion was that patient must have completed three full doses of recombinant HBV vaccination as evidenced by EPI/vaccination card. Children with chronic hepatitis B infection, immunodeficiency or on immunosuppressant drugs and chronic diarrhea due to other causes were excluded.

Clinical data was compiled for each subject from a review of previous medical and vaccination records. Age, sex, immunization status especially HBV vaccination (including timing of immunizations), age of diagnosis for CD, results of celiac panel if it was done within 2 months before the antibody testing (as a reflection of adherence to gluten-free diet in CD group), medication (current and past), coexisting medical condition and family history were recorded.

Patients diagnosed with CD were tested for hepatitis B surface antibody (HbsAb). Samples with antibody titers of ≥ 10 mIU/ml were taken as positive. HbsAb levels less than 10 mIU/ml were considered a vaccine non-responsive. These children were given one extra shot of HBV vaccine. Data was entered on specific proforma which included chronological age, age at diagnosis, sex, weight, height, presenting complaint, co-morbid condition (diabetes mellitus, hypothyroidism, epilepsy, dermatitis herpetiformis) anti tTG-IgA level, histopathology (if biopsy done), HbsAb level along with both mother and father education. Data was analyzed using SPSS version 20.0. Chi square test was used for comparison of different variables with *P*-value less than .05 considered as statistically significant.

Results

Out of 38 diagnosed cases of CD, 39.5% (n=15) were male and 60.5% (n=23) were female. Mean age of children was 8.32 ± 3.26 years with an age range of 3-14 years. Mean values of age at diagnosis, height, weight, anti tTG-IgA and HbsAb levels are given in table I. The most common presenting complaint for which patient visited the OPD was chronic diarrhea (n=21; 55.3%) followed by pallor (n=10; 26.3%) (Table II). Regarding age at diagnosis, almost half of the children (n=20; 52.6%) were diagnosed in >5 years to 10 years age group followed by <5 years (n=11; 28.9%) and >10 years age group (n=7; 18.4%).

Table I: Baseline characteristics of children with celiac disease

Characteristics	Min	Max	Mean \pm SD
Age (years)	3.00	14.00	8.32 \pm 3.26
Weight (kg)	6.90	42.00	19.18 \pm 8.15
Height (cm)	70.00	157.90	113.46 \pm 21.52
Age at diagnosis (years)	2.00	14.00	7.51 \pm 3.57
Anti tTG-IgA (IU/ml)	11.90	800.00	242.02 \pm 173.09
HbsAb level (mIU/ml)	0.10	62.71	11.21 \pm 17.42

Most of the mothers (71.1%) were educated up to tenth grade (Secondary school/High school level) while most of the fathers (71.1%) had higher level of education (Eleventh grade/Intermediate or higher).

Most of the children with CD (n=32; 84%) had higher levels of anti tTGA-IgA than the cut-off value of 150 IU/ml. Small bowel biopsy was done in all patients with anti tTG-IgA levels <150 IU/ml, except one patient. In majority of patients with anti tTG-IgA levels >150 IU/ml, small bowel biopsy was not done. Histopathology of small bowel showed increased epithelial lymphocytes along with villous atrophy.

Complaints	Frequency n (%)
Pallor	10 (26.3)
Failure to thrive	1 (2.6)
Diarrhea	21 (55.3)
Constipation	3 (7.9)
Abdominal distension	1 (2.6)
Short stature	2 (5.3)
Total	38 (100)

There was significant relationship between anti tTG-IgA levels and histopathology findings ($P=.001$). HbsAb levels were less than 10.0 IU/ml in majority of patients, with 28 (73.7%) patients having antibody less than protective levels and only 10 (26.3%) patients having levels in the protective range. In children with anti tTG-IgA level more than 150 IU/ml, majority of patients (71.87%) were having anti HbsAb levels less than 10 mIU/ml ($P=.559$).

Discussion

In this study we report lower levels of HbsAb (<10.0 IU/ml) in 73.7% of CD children (n=38) with a mean age of 8 years in our tertiary care set-up at Abbottabad, Pakistan. Some of the affected children can present with involvement of endocrine, neural, liver, heart, and skin as atypical presentation of CD. Autoimmune diseases are more prevalent in children with CD as compared to normal healthy children.¹⁰ Hepatitis B viral infection is very much prevalent in our part of the country and children with less levels of protective HbsAb are prone to infection despite completing the series of HBV vaccination. Inclusion of HBV vaccine in national immunization program has led to a decrease in chronic HBV carriers and liver cancer associated with it.^{11,12}

Sparks et al.¹³ studied children with CD recorded in the institutional registry and developed a Celiac Care Index. The common presentation was iron

deficiency (41%) in their study. We reported history of progressive pallor in 26.3% of the patients. Non immunity to HBV in their study was comparable to our findings (70% versus 73.7%). Another study by Walkiewicz-Jedrzejczak et al.¹⁴ included children with CD who had completed primary HBV vaccination. More than half of the children (58%) in this study did not have protective antibody levels in response to HBV vaccine. Ertekin et al.¹⁵ also compared response to standard HBV vaccine in CD and healthy children. Male and female distribution of celiac disease was comparable to our study. HBV vaccine non-responders were 38.5% as compared to 73.7% in our study. Snyder et al.¹⁶ in their expert-informed recommendations for management of CD in children endorsed routine screening for HB immunization status. Most of the studies have shown that 30-70% of children with CD are non-responsive to HBV vaccine.¹⁶ Zifman et al.¹⁷ retrospectively evaluated CD children for the effect of gluten free diet on HbsAb response. They found no relation of gluten free diet on pre- and post HbsAb levels. Urganci and Kalyoncu¹⁸ studied hepatitis A and hepatitis B vaccine response in children with CD. Children who got HBV vaccine, the overall response rate in protective range was 70%. This is in sharp contrast to our reported figure of 26.3%. Though the exact reason for this difference in response is not known, genetic factors may be responsible and should be explored. In a study by Filippelli et al.¹⁹ patients were grouped according to age. Majority (48.9%) of their patients were in age category of 0 to 5.5 years at diagnosis while in our study majority (52.6%) of patients were between 5.1 to 10 years of age. This may be due to lack of education of parents specifically mothers, as most of them were educated up to high school level (10th grade) or even less. In our setup most of the children are brought to hospital by mothers. In Filippelli et al.¹⁹ study the overall response rate of HBV vaccine in all three age groups was 69.37%, while in our study group it was only 26.3%. In study by Leonardi et al.²⁰ 50% of patients did not show response to

HBV vaccine. In our study, 73.7% patients were not having HbsAb in protective range. This difference can also be attributed to genetic differences between the two populations. Rouseff et al.²¹ included 133 children with celiac disease in their study with 35% affected males and 55% were non-responsive to HBV vaccine. Rouseff et al. gave booster shot of HBV and the non-response rate reduced from 55% to 23%.

Anania et al.²² recommended practical guidelines for vaccination of children with CD as HBV vaccine response in children with CD is less and it may be related to HLA or gluten exposure at the time of vaccination. Vitaliti and colleagues²³ in their mini review highlighted the possible factors in non-responsiveness of CD children to HBV vaccine and emphasized for the alternate schedule of HBV vaccine. Heshin-Bekenstein et al.²⁴ compared pre-S vaccine with standard HBV vaccine in children who were known cases of CD. Pre-S vaccine is recombinant hepatitis B vaccine, containing major S protein and minor pre-S1 and pre-S2 proteins of HBV coat. These children completed their primary immunization course and their HbsAb were not in the protective range. The response to standard HBV vaccine was 87% after one month as compared to pre-S vaccine, whose response rate was 98%. In our study, we gave one extra shot of standard HBV vaccine.

A major limitation of our study was checking HBsAb level only once due to high cost of the test. So, it is not clear if our population is responsive to the extra shot of hepatitis B vaccine. Another limitation in this study was that we only included children with CD and no comparison was done with healthy population. Therefore, we cannot comment on the actual difference of response between diseased and non-diseased children. Due to rare availability and high cost, HLA DQ2 test was not done. This study gave insight in to the prevalence of non-responsiveness to hepatitis B vaccine in children

with CD who are prone to be infected with hepatitis B virus in our population.

Conclusion

Children with celiac disease are less responsive to hepatitis B vaccine. These children should be tested for HbsAb levels, apart from monitoring adherence to gluten free diet and surveillance for other autoimmune diseases.

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