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Responsiveness of children with celiac disease to different hepatitis B vaccination protocols

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Background/aims: *We aimed to compare the response rates to hepatitis B virus vaccination in the first year of life, using two different immunization protocols, in children with celiac disease.* ***Methods:*** *Study Group 1 included patients with celiac disease who received 10 µg of hepatitis B vaccine intramuscularly at birth (0), 2 and 9-12 months of life. Group 2 included those who received hepatitis B vaccine at 0, 1 and 6 months of life. Healthy children were divided into two control groups according to the above schedules.* ***Results:*** *The total study group included 64 patients and 49 healthy controls. Celiac patients were found to have lower response rates with respect to controls (78.1% vs. 95.9%, respectively). The difference in response rates in the two patient groups was not statistically significant.* ***Conclusions:*** *The response rates of celiac patients to the two different hepatitis B vaccination schedules showed no statistically significant difference.*

Key words: Celiac disease, children, hepatitis B vaccination, different protocols, response rates

Çölyak hastalığı olan çocuklarda farklı hepatit B aşılama protokollerine cevap

Amaç: *Çölyak hastalığı olan çocuklarda hayatın ilk 1 yılı içerisinde farklı Hepatit B aşı protokolleri ile aşılama sonrası aşı cevabının değerlendirilmesi amaçlanmıştır.* ***Yöntem:*** *Çölyak hastalığı olan çocuklardan; doğumda, doğumdan 2 ay sonra, 9-12. aylarda intramüsküler 10 µgram Hepatit B aşısı ile aşılanlar bir grup, doğumda ve doğumdan 6 ay sonra aşılananlar bir diğer çalışma grubu olarak belirlendi. Aynı aşılama şemaları ile aşılanan sağlıklı çouklar da kontrol grubu olarak değerlendirildi.* ***Bulgular:*** *Çalışma grubunda 64 hasta ve 49 sağlıklı çocuk mevcuttu. Çölyak hastalarında kontrol grubuna göre aşı cevabının daha düşük olduğu saptandı (%78,1'e karşılık %95,9). İki hasta grubu arasında ise cevap oranlarında istatistiksel olarak anlamlı değişiklik bulunmadı.* ***Sonuç:*** *Çölyak hastalarında farklı Hepatit B aşı protokollerinde aşı cevabı arasında istatistiksel fark yoktur.*

Anahtar kelimeler: Çölyak hastalığı, çocuk, Hepatit B aşısı, farklı protokoller, cevap hızı

INTRODUCTION

Celiac disease (CD) is a common autoimmune disease characterized by permanent intolerance to ingested gluten, which results in immune-mediated injury of the small bowel mucosa. Genetic, environmental and immunological factors are responsible for the disease. Susceptibility to CD is determined, in part, by a common human leukocyte antigen (HLA) association; specifically, the major histocompatibility complex class II antigen DQ2, which is present in 86% to 100% of the patients (1).

Hepatitis B virus (HBV) infection is one of the most important public health problems worldwide. HBV infection acquired during the perinatal, infancy and early childhood periods is a major cause of chronic liver disease and liver cancer (2). Hepatitis B vaccine is highly effective and safe, and it can prevent the morbidity and occasional mortality associated with infection (3). For this reason, HBV vaccine is considered as the main strategy in the control of the infection and viral transmission. HBV vaccine was introduced into clinical practice

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in the early 1980s, and in 1998, the hepatitis B vaccination was included in the Expanded Immunization Program in Turkey. At its onset, the HBV vaccine had been routinely administered at birth (0), 2 and 9-12 months. The immunization schedule was changed in 2002, with the vaccine being administered at 0, 1 and 6 months of life. The incidence of unresponsiveness to HBV vaccine in the general population varies between 4% and 10%. Many non-genetic factors, including the site and route of administration, older age, male gender, being overweight, immunosuppression, immunodeficiency, smoking habit, and others, are known to be associated with unresponsiveness (4). Previous studies have demonstrated that the HLA phenotype is considered the most important genetic marker of unresponsiveness to HBV vaccine. Homozygotes and heterozygotes for HLA-B8, DR3 and DQ2 were found to be exclusively in the non-responder group with respect to responders (5,6).

It is well known that the response rate to HBV vaccine in celiac patients is lower compared to the healthy population, but there is no knowledge about the effect of different immunization schedules on the response rate and anti-HBs titers in patients with CD.

The aim of this study was to determine the response rates to HBV immunization in children with CD who were previously vaccinated according to the two aforementioned HBV immunization schedules and to compare the response rates between the different schedules and between CD patients and healthy controls.

MATERIALS AND METHODS

Patients and controls

The study was carried out at Hacettepe University Medical Faculty, Pediatric Gastroenterology, Hepatology and Nutrition Department. The study group (Group 1) consisted of newly or previously diagnosed CD patients diagnosed according to the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria (7). The control group (Group 2) consisted of healthy children who were admitted to well-child clinics, all of whom were negative for blood autoantibody markers of CD. Group 1 was divided into two subgroups based upon the immunization schedule as Group 1A: CD patients administered 10 µg of HBV vaccine intramuscularly at 0, 2 and 9-12 months of life, and Group 1B: CD patients administered 10 µg of HBV vaccine intramuscularly at 0, 1 and 6 months of life. Healthy children who had been vaccinated with either of the above schedules were grouped as 2A and 2B, respectively.

Inclusion and exclusion criteria

Inclusion criteria required that subjects must have completed three full doses of recombinant HBV vaccination at least four weeks before enrollment into the study. Patients who were born from HBsAg-positive mothers, who had immunodeficiency, chronic renal failure, hepatitis C virus infection, chronic liver disease, poor weight gain in the first 6 months of life, prematurity and low birth weight (<2000 g) in birth history, who were using steroids, or who were diagnosed as CD before the implementation of the HBV vaccination protocol were excluded from the study.

Determination of serum Anti-HBs titers

Subjects in both groups were assessed for their hepatitis B immunization status. Anti-HBs antibodies were measured by enzyme-linked immunosorbent assay (ELISA). A seroconversion rate was defined by anti-HBs titers >10 IU/L. Patients with an anti-HBs titer <10 IU/L were regarded as unresponsive, between 10 and 100 IU/L as weakly responsive, and >100 IU/L as responsive (5).

Statistics

Demographic variables between groups were compared by chi-square and t-tests. Grouped variables between the study and control groups were compared using chi-square test. Anti-HBs titers between the two groups were compared using t-test. Pearson correlation coefficient was calculated for bivariate correlations. SPSS version 15.0 was used for all the statistical analysis, and statistical significance was set at $p<0.05$.

RESULTS

Group 1 comprised 64 children (37 female, 27 male; mean age 4.69±2.31 years) and Group 2 consisted of 49 children (23 female, 26 male; mean age 5.45±2.92 years). The groups were similar in terms of gender and age. Demographic data of the subjects are shown in Table 1. Celiac patients were found to have lower response rates when compared to healthy controls (Table 2). There were no differences in terms of response rates within CD patients (Groups 1A vs. 1B) or within healthy controls (Groups 2A vs. 2B). Anti-HBs titers were lower in CD patients than healthy controls. Anti-

Table 1. Comparison of gender and age between subgroups

	Group 1 (n=64)	Group 2 (n=49)	P value
Gender (F/M)	37/27	23/26	>0.05
Age (years)	4.69±2.31	5.45±2.92	>0.05
	Group 1A (n=45)	**Group 1B (n=19)**	**P value**
Gender (F/M)	27/18	10/9	0.5
Age (years)	5.2±2.3	3.3±1.4	0.01
	Group 2A (n=29)	**Group 2B (n=20)**	**P value**
Gender (F/M)	18/11	5/15	0.01
Age (years)	7.2±2.3	2.8±1.1	<0.001

Group 1: *Patient group;* ***Group 2:*** *Control group.* ***Group 1A:*** *Patients vaccinated at 0, 2 and 9-12 months of life,* ***Group 1B:*** *Patients vaccinated at 0, 1 and 6 months of life,* ***Group 2A:*** *Healthy children vaccinated at 0, 2 and 9-12 months of life,* ***Group 2B:*** *Healthy children vaccinated at 0, 1 and 6 months of life.*

HBs titers and time passed since last vaccine dose are shown in Table 3. There was no difference in terms of HBV vaccination responsiveness between girls and boys in the entire study population (113 children).

DISCUSSION

Our results have shown that the response rate to HBV vaccine and anti-HBs titers in CD patients who completed the HBV vaccination before one year of age were significantly lower compared to healthy controls. The response rates of CD patients to two diverse HBV vaccination schedules did not differ between the schedules; however, they were significantly lower compared to their counterparts in healthy controls.

It is well known that HBV vaccine is a highly effective and safe means of protection from HBV infections. However, approximately 4% to 10% of healthy immunocompetent subjects do not mount an antibody response (4). In this study, the rate of unresponsiveness in healthy subjects was 4.1%, which is compatible with former reports. Previous studies reported that the response rates to HBV vaccine in patients with CD were lower than those of healthy individuals. Noh et al. (8) reported that 13 of the 19 adult patients who were either homozygous or heterozygous for HLA DQ2 did not respond to HBV vaccine. They postulated that hepatitis B non-responders might have failure of induction of type 2 helper cell response - needed for B cell differentiation - and formation of memory B cells needed for immunization. CD patients may have a failure of induction of humoral immune response, needed for development of long-term immunity, though the relevant mechanism is as yet unclear. Nemes et al. (9) observed that the seroconversion rate after HBV vaccination was significantly lower among untreated versus treated and

Table 2. Responsiveness to hepatitis B vaccination

Groups	Number (n)	Unresponsive (Anti-HBs <10 IU)	Weakly responsive (Anti-HBs 10-100 IU)	Responsive (Anti-HBs >100 IU)	P value
Group 1	64	14 (21.9%)	21 (32.8%)	29 (45.3%)	**0.001**
Group 2	49	2 (4.1%)	9 (18.4%)	38 (77.6%)	
Group 1A	45	11 (24.4%)	14 (31.1%)	20 (44.4%)	**0.024**
Group 2A	29	2 (6.9%)	5 (17.2%)	22 (75.9%)	
Group 1B	19	3 (15.8%)	7 (36.8%)	9 (47.4%)	0.056
Group 2B	20	0 (0.0%)	4 (20.0%)	16 (80.0%)	

Group 1: *Patient group;* ***Group 2:*** *Control group.* ***Group 1A:*** *Patients vaccinated at 0, 2 and 9-12 months of life,* ***Group 1B:*** *Patients vaccinated at 0, 1 and 6 months of life,* ***Group 2A:*** *Healthy children vaccinated at 0, 2 and 9-12 months of life,* ***Group 2B:*** *Healthy children vaccinated at 0, 1 and 6 months of life*

Table 3. Anti-HBs titers according to the groups

Group	Number	Anti-HBs titers	P value	Time passed since last vaccine dose	P value
Group 1	64	202.4±276.9	0.001	3.8±2.2	0.09
Group 2	49	409.0±354.8		4.6±2.8	
Group 1A	45	182.0±261.8	0.004	4.3 ±2.3	0.001
Group 2A	29	399.3±358.9		6.4±2.3	
Group 1B	19	250.5±311.9	0.1	2.7±1.3	0.1
Group 2B	20	423.1±357.6		2.2 ±1.0	

Group 1: *Patient group;* ***Group 2:*** *Control group.* ***Group 1A:*** *Patients vaccinated at 0, 2 and 9-12 months of life,* ***Group 1B:*** *Patients vaccinated at 0, 1 and 6 months of life,* ***Group 2A:*** *Healthy children vaccinated at 0, 2 and 9-12 months of life,* ***Group 2B:*** *Healthy children vaccinated at 0, 1 and 6 months of life*

diet-compliant subjects with CD or control subjects. They suggested that both HBsAg protein fragments and gliadin peptides bind to HLA-DQ2 molecules, and their competition might result in a defective antibody response against the recombinant HBV vaccine in active CD. In addition, they found that untreated adolescent CD patients had decreased humoral immunity to the HBV vaccine. However, after the diagnosis, patients who complied with the gluten-free diet had similar vaccine response rates to those of healthy adolescents. Park et al. (10) reported that a significantly higher proportion of subjects in the CD group (53.9%) failed to respond to HBV vaccine compared to controls (11.1%). In addition, 68.8% of the patients with CD who completed the HBV vaccination before one year of age did not develop anti-HBs. Conversely, 3 of 10 (30%) patients with CD who completed vaccination at or after one year of age failed to develop anti-HBs. Ertem et al. (11) reported that the response to HBV vaccine in celiac children who were compliant with a gluten-free diet was not different from that of healthy controls. They suggested that compliance with the gluten-free diet may ameliorate the immune response to HBV vaccine in children with CD.

Various studies have investigated the protectiveness and the antibody titers of different HBV vaccine schedules in healthy individuals and high-risk patients (12-15). Grisha et al. (14) investigated the antibody response and compared the 0, 1 and 2 months vaccination schedule to the 0, 1 and 6 months schedule. They found that the latter protocol produced higher antibody titers. Jlig et al. (15) evaluated and compared three different hepatitis B vaccination protocols (0, 1 and 2 months; 0, 1 and 6 months; and 0, 1, 2, and 12 months) in terms of antibody titers and protection rates. They found that for achieving a high anti-HBs concentration and for guaranteeing its long-lasting persistence, vaccination at 0, 1, 2, and 12 months seemed preferable to vaccination at 0, 1 and 6 months. They also emphasized that for individuals at high risk of HBV infection, vaccination at months 0, 1, 2, and 12 months might be considered for obtaining an optimal early seroconversion as well as for long-term protection. This study is the first to investigate the effect of different immunization schedules on the response rate and anti-HBs titers in children with CD. Our results have shown that the two vaccination protocols demonstrated similar results in terms of protection (anti-HBs >10 IU/L).

In conclusion, the different HBV immunization schedules implemented in the first year of life seem to be similar in terms of protection. Antibody response in children who were immunized with HBV vaccine in the first year of life and later developed CD seem to be lower regardless of the immunization schedule. For this reason, even if routine immunization schedules for HBV are followed, anti-HBs titers should be determined in CD patients at the time of diagnosis, and appropriate measures, including re-immunization, should be considered. The effect of diet compliance on the anti-HBs titers should also be investigated and, if necessary, guidelines for anti-HBs titer follow-up and re-vaccination for CD patients should be developed.

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