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Evaluation of hepatitis B seroprevalence and hepatitis B antibody response in children with celiac disease

Çölyak hastalığı olan çocuklarda hepatit B seroprevalansı ve hepatit B antikor yanıtının değerlendirilmesi

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Background and Aims: *It is already known that the response to recombinant hepatitis B virus vaccine is low in some autoimmune diseases. However, this is still controversial. Although 90-95% of the pediatric population responds to hepatitis B vaccination, it is reported that this rate may be lower in celiac patients. In our study, the researchers aimed to determine the prevalence of the hepatitis B virus in celiac patients and the vaccine response rates in vaccinated celiac patients.* ***Materials and Methods:*** *The study included 264 celiac patients and 264 control patients aged 2-18 years who applied to the clinic between 2020 and 2024. Demographic, and anthropometric characteristics and hepatitis B serologies were examined in the patients, and hepatitis B vaccination rates and vaccine responses were determined.* ***Results:*** *Among the patients included in the study, 346 (60.9%) were female, 182 (39.1%) were male, and the mean age of the patients was 10.83 ± 6.9 years. All patients were fully vaccinated according to the standard vaccination schedule. While 147 (55.6%) of the celiac patients had a vaccine response, 117 (44.3%) had an inadequate vaccine response. In the control group, 163 (61.7%) of the patients had a vaccine response, while 101 (38.2%) had an inadequate vaccine response. Hepatitis B surface antigen positivity was determined in 4 patients in the celiac group, while hepatitis B surface antigen positivity was detected in only 1 patient in the control group.* ***Conclusion:*** *Considering that chronic hepatitis B virus carriage is more widespread in celiac patients, the importance of vaccination against hepatitis B virus increases even more. For this reason, it is of great importance to monitor the vaccine response of all celiac patients following vaccination and to include cases that do not develop a vaccine response in the revaccination program.*

Key words: *Celiac disease, hepatitis B, vaccination*

Giriş ve Amaç: *Bazı otoimmün hastalıklarda rekombinant hepatit B virüs aşısına karşı yanıtın düşük olduğu bilinmektedir. Fakat bu konu hala tartışmalıdır. Çocuk popülasyonun %90-95'i hepatit B aşılamasına yanıt verirken, çölyak hastalarında bu oranın daha düşük olabileceği bildirilmektedir. Çalışmamızda çölyak hastalarında hepatit B virüs prevalansını, aşılanmış çölyak hastalarında aşı yanıt oranlarını tespit etmeyi amaçladık.* ***Gereç ve Yöntem:*** *Çalışmaya 2020 ile 2024 yılları arasında polikliniğe başvuran 2-18 yaş aralığında 264 çölyak hastası ve 264 kontrol hastası alındı. Hastalarda demografik, antropometrik özellikler, hepatit B serolojileri bakıldı. Hepatit B aşılanma oranları ve aşı yanıtları belirlendi.* ***Bulgular:*** *Çalışmaya alınan hastaların 346'sı (%60.9) kadın ve 182'si (%39.1) erkek olup hastaların ortalama yaşı 10.83 ± 6.9 yıl idi. Hastaların tümünün, standart aşı takvimine göre, aşıları tam idi. Çölyak tanılı olguların 147'sinde (%55.6) aşı yanıtı var iken 117'sinde (%44.3) aşı yanıtı yetersiz bulundu. Kontrol grubunda ise, olguların 163'ünde (%61.7) aşı yanıtı var iken 101'inde (%38.2) aşı yanıtı yetersiz idi. Çölyak grubunda 4 hastada hepatit B yüzey antijeni pozitifliği saptanırken kontrol grubunda sadece 1 hastada hepatit B yüzey antijeni pozitifliği saptandı.* ***Sonuç:*** *Çölyak hastalarında kronik hepatit B virüsü taşıyıcılığının daha fazla olduğu düşünüldüğünde, hepatit B virüsüne karşı bağışıklamanın önemi daha da artmaktadır. Bu nedenle tüm çölyak hastalarının aşılanma sonrası aşı yanıtının takip edilmesi ve aşı yanıtı gelişmeyen olguların tekrar aşılama programına alınması büyük önem arz etmektedir.*

Anahtar kelimeler: *Çölyak hastalığı, hepatit B, aşılanma*

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune systemic disease caused by a T cell-mediated immune mechanism that is triggered by gluten contained in grains such as wheat, barley, and rye in genetically predisposed individuals. The frequency of the disease varies geographically. The highest incidence is in countries where wheat is an important part of daily nutrition, such as Turkey, Western Europe, North America, and Australia. Environmental, immunological, and genetic factors play a role in its pathogenesis (1-3).

The correlation between celiac disease and environmental factors other than gluten has not been fully elucidated yet. Also, inadequate breastfeeding during infancy, viral and other infectious diseases, and smoking may contribute to the onset of the disease (4). Also, it is reported that hepatotropic viruses, together with gluten, may trigger pathophysiological processes that cause mucosal inflammation and autoimmune events during the disease (5).

Previous studies report that the frequency of chronic viral hepatitis in celiac patients is higher than in the normal population (6,7). Also, vaccination against hepatitis B in childhood is an effective and reliable means of protection against widespread hepatitis B virus (HBV) infections, however, it has been reported that the vaccine response is lower in celiac patients (5,8).

The purpose of the present study was to determine the prevalence of the hepatitis B virus in celiac patients and the hepatitis B response rates in celiac patients vaccinated according to the standard vaccination schedule.

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MATERIAL and METHODS

Selection of Patients

The study included 264 patients who were diagnosed with celiac disease and 264 healthy children without celiac disease who were followed up by the Health Sciences University Diyarbakir Gazi Yaşargil Training and Research Hospital, Pediatric Gastroenterology Polyclinic between November 2020 and December 2024. The ages of the patients included in the study ranged from 2 to 18 years. Since it may affect the antibody response, those with a systemic disease or those receiving treatment for systemic disease, those with another inflammatory or infectious disease, those with malignancy, those with renal failure, cardiac failure and liver failure, diabetes mellitus, inflammatory bowel disease, and hematological diseases were excluded from the study. In all groups, only patients who had received 3 doses of hepatitis B vaccine were included in the study and patients who had received additional doses or incomplete doses were excluded from the study.

Data Evaluation

Demographic data (i.e., age, sex), vaccination status, hepatitis B surface antigen (HBsAg), and anti-HBsAg of all patients were recorded. The endoscopic appearance and histopathological data of the patients were documented.

Biochemical Measurements

Biochemical parameters were measured from antecubital venous blood samples that were taken in the morning hours following an 8-hour fast.

Endoscopic Evaluation

Endoscopies of the patients were performed by using a Fujinon EG530WR endoscopy device at the Gazi Yasargil Education and Research Hospital, Gynecology and Pediatrics Hospital Endoscopy Unit. Verbal and written consent was obtained from the families before endoscopy. All patients were fasted for 6 hours before endoscopy, and following local pharyngeal xylocaine anesthesia, the patients were sedated with 0.1 mg/kg midazolam and 1 mg/kg ketamine, and then the endoscopic procedure was performed. During endoscopy, the esophagus, stomach, and duodenum were examined in detail and multiple biopsies were taken from different sites for the diagnosis of celiac disease, as previously reported.

Histopathological Evaluation

Endoscopically obtained esophageal, corpus, antrum, and duodenum biopsies were sent to the pathology laboratory in 10% formaldehyde. Following routine tissue follow-up procedures, paraffin-embedded tissue samples were cut into 5-micron thicknesses, stained with routine hematoxylin-eosin (H-E), and evaluated under a light microscope. Histopathological evaluation was performed according to the Marsh classification. The diagnosis of CD was based on the characteristic histological finding of increased intraepithelial lymphocytes, villous atrophy, and crypthyperplasia classified according to the standard classification proposed by Marsh (2,9)

Hepatitis B Serology

Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B e-antigen (HBeAg), hepatitis B virus e-antibody (Anti-HBe), immunoglobuline M antibody against hepatitis B core antigen (anti-HBc IgM), immunoglobuline G antibody against hepatitis B core antigen (anti-HBc IgG), and when necessary antibodies against hepatitis delta virus (Anti-HDV), HBV-DNA (Amplicor HBV MonitorTM test, Roche Diagnostic Systems, Inc., Branchburg, NJ) were investigated. Enzyme-Linked Immunosorbent Assay (ELISA) method was employed to evaluate HBsAg, HBeAg, anti-HBe, anti-HDV, anti-HCV, and anti-HIV tests in all patients, HBV-DNA was tested using quantitative polymerase chain reaction (PCR).

Seroconversion or antibody response was taken as anti-HBs titer > 10 IU/L. When the anti-HBs titer was < 10 IU/L, it was accepted as unresponsive or seroconversion negative.

Ethics Statement

All participants provided written consent to participate in the study. Ethical approval for the study was obtained from our hospital's Ethics Committee (No: 287, Diyarbakır, Turkey). All procedures followed the ethical standards of our institution's human experimentation committee and the Declaration of Helsinki. Written informed consent forms were obtained from all participants, who were evaluated by a gastroenterologist and included in the study.

Statistical Analysis

The normality of the distribution of continuous variables was tested by the Shaphiro-Wilk test. The Mann-Whitney U test was used for non-normal data in the comparison of two independent groups and the Wilcoxon test was used to compare before and following measurements for non-normal data. The Chi-Square test was used to evaluate the relation between categorical variables. Statistical analysis was performed with SPSS for Windows version 24.0 and a p-value < 0.05 was accepted as statistically significant.

RESULTS

Among the patients who were included in the study, 346 (60.9%) were female, 182 (39.1%) were male, and the mean

Table 1. Vaccine response rates in the celiac and control group cases

	Patients with celiac disease (n; 264)	Control Group (n; 264)	P
Anti-HBsAg > 10 IU/L	147 (%55.6)	163 (%61.7)	0.294
Anti-HBsAg < 10 IU/L	117 (%44.4)	101 (%38.3)	

age of the patients was 10.83 ± 6.9 years. All patients were fully vaccinated according to the standard vaccination schedule. There were no significant differences between the age and gender distribution of the cases.

When the vaccination status was evaluated, all patients in the celiac and control groups had received a total of three doses of the hepatitis B vaccine regularly according to the standard vaccination schedule. Although the number of those who responded to the vaccine (anti-HBs ≥ 10 I/U) in the celiac patients was 147 (55.6%), the number of those who did not respond to the vaccine was 117 (44.3%). The number of those who responded to the vaccine (anti-HBs ≥ 10 I/U) was 163 (61.7%) and the number of those who did not respond to the vaccine was 101 (38.2%) in the control group (Table 1). HBsAg positivity was detected in 4 cases in the celiac group, but it was detected in only 1 case in the control group.

DISCUSSION

HBV infection is a significant public healthcare concernon a global scale. However, the occurrence of chronic liver disease, morbidity, and mortality have decreased significantly with vaccination. After the implementation of mass immunization programs recommended by the World Health Organization in 1991, the incidence of HBV infection among infants, children, and adolescents decreased significantly in many countries. In previous studies, although the immune response rate to HBV vaccination was found to be around 90%, it was reported that the immune response rate to HBV vaccine in celiac patients was 4%-10% lower than in the healthy population (10,11). In our study, similar to the literature, the vaccine response rate in celiac patients was 6.1% lower than in the healthy control group. The ability to respond to recombinant HBV vaccine has been associated with many genes. In this respect, it is accepted that the most important specific genes are human leukocyte antigen (HLA) haplotypes. It has been thought that the high prevalence of hepatitis and the low vaccine response rate in celiac patients may be related to the unresponsiveness of the immune system (12). In a study conducted in our country in the adult age group, the prevalence of HBV was found to be 2-4%. When this rate is considered, it is seen that there is a moderate increase in the prevalence of chronic hepatitis B in celiac patients (13).

In previous years, although it varied among regions, HBsAg seroprevalence was found to be between 3.9-12.5%, and anti-HBs seroprevalence was found to be between 20.6 - 52.3% in our country (14,15). In previous studies conducted in later years, Aypak et al. found HBsAg positivity at 0.0% and anti-HBs positivity at 66.4% in a study that was conducted in Ankara between 2010 and 2011; Kaya et al. found HBsAg positivity at 0.2% and anti-HBs positivity at 71.3% in another study conducted in Van; Ayvaz et al. found HBsAg positivity at 0.16% and anti-HBs positivity at 73.9% in a previous study conducted in Sivas in 2008 (16-18). In another study conducted by Bardella et al., it was reported that HBsAg positivity was 2.5% in celiac patients and that there may be a relationship between celiac disease and HBV infection (19). Similarly, in another study conducted by Gamal et al., HBs Ag positivity was detected in 9.9% of the cases and this rate was reported to be significantly higher than the prevalence of chronic hepatitis B in the country (6). In our study, HBsAg positivity was detected in 4 (1.9%) of the celiac cases, while only 1 case of the control cases was found to be HBsAg positive. These results show that HBsAg positivity is higher in celiac cases than in the normal population.

It is speculated that the HLA DQ2 genotype plays a role in the development of low immune response to recombinant HBV vaccine (20). Also, other studies reported that gluten intake during vaccination may have a possible effect (21). For this reason, vaccine non-response will be seen more frequently in those who do not comply with a gluten-free diet.

In conclusion, although it was not statistically significant in the present study, the researchers found that celiac cases had lower vaccine response to the HBV vaccine compared to the control group. Also, chronic HBV carriage was observed to be higher in cases diagnosed with celiac disease. Considering that chronic HBV carriage is higher in celiac patients, the importance of vaccination against HBV increases even more. For this reason, it is of great importance to monitor the vaccine response of all celiac patients following vaccination and to include those who do not develop a vaccine response in the revaccination program.

Ethics: *All participants provided written consent to participate in the study. Ethical approval for the study was obtained from Gazi Yaşargil Training and Research Hospital, Clinical Research Ethics committee (No: 287, Diyarbakır, Turkey).*

Disclosure statements: *The authors declare no conflicts of interest.*

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Authorship contribution: *M.A. and A.O. developed the study protocol, screened and enrolled the patients, evaluated the outcomes, preliminarily analyzed the data, and wrote the manuscript. M.A. and A.O. developed the study protocol and analytical framework for the study and contributed to the writing of the manuscript. M.A., A.O., and M.A. screened the patients. M.A. and A.O. supervised the design and execution of the study, performed the final data analyses, and contributed to the writing of the manuscript. All authors have read and approved the final manuscript.*

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