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EVALUATION OF HEPATITIS A AND B VACCINE ANTIBODY RESPONSE IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES MELLITUS

TİP 1 DİABETES MELLİTUSLU PEDİATRİK HASTALARDA HEPATİT A VE B AŞISI ANTİKOR YANITININ DEĞERLENDİRİLMESİ

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ABSTRACT

Aim: Type 1 Diabetes; in addition to blood glucose dysregulation, it also progresses with secondary immune dysregulation. Hepatitis A and hepatitis B viruses can therefore cause severe infection in children with type 1 diabetes.

Material and Methods: In this cross-sectional study, pediatric patients with type 1 diabetes mellitus (T1D), aged 3-18, with completed vaccination schedules were involved. Hepatitis B (hepB) vaccine protection was evaluated by measuring anti hepatitis B surface antigen (anti-HBS), and hepatit A (hepA) immunity is measured by anti-hepatitis A virus immunoglobulin G (Anti-HAV IgG) level.

Results: Three hundred and forty-five patients and 250 controls, totally 595 cases were included. The age of diabetic cases was 12.7±4.0 years and the age of control group was 11.9±4.7 years (p=0.027). While anti-HBS positivity was 51.3% (177 patients) in T1D children, it was higher with 59.4% (149 patients) in the control group (p=0.047). The number of participants who received HepA vaccine was 230 (38.6%). Anti-HAV IgG positivity was similar in T1D and control groups (173 (50.2%) and 136 (54.4%), respectively, p=0.378). Anti-HAV IgG positivity was 29.4% (n:107) in 365 participants who were not vaccinated against hepA, while this rate was 90.8% (n:209) in 230 children who were vaccinated (p<0.001).

Conclusion: In T1D patient group, while adequate immune response was achieved against hepA virus after vaccination, insufficient immune response was observed against hepB virus despite vaccination. Anti-HAV IgG testing in this risky group of chronic patients who have not been vaccinated with hepA vaccine at the time of diagnosis may be taken into account. In all patients, regardless of vaccination status, we recommend routine monitoring of anti-HBS levels, this screening should be included in the guidelines, and a booster dose of vaccine for patients with inadequate antibody response should be applied.

Keywords: Anti-HBS, Anti-HAV IgG, Pediatric, Type 1 Diabetes Mellitus.

ÖZET

Amaç: Tip 1 Diyabet hastalığı; kan şekeri disregülasyonunun yanı sıra sekonder immün disregülasyon ile de seyretmektedir. Hepatit A ve hepatit B virüsleri, tip 1 diyabetik çocuklarda bu nedenle şiddetli enfeksiyona neden olabilir.

Gereç ve Yöntemler: Kesitsel tipte olan bu çalışmaya, 3-18 yaş arası tip 1 diabetes mellitus (T1D) tanısı olan, aşı çizelgeleri tamamlanmış pediatrik hastalar dahil edildi. Hepatit B'ye (hepB) karşı immunite durumu anti hepatit B yüzey antijeni (anti-HBS), hepatit A'ya karşı (hepA) immunite durumu ise anti-hepatit A virüsü immünoglobulin G (Anti-HAV IgG) düzeyi ölçülerek değerlendirildi.

Bulgular: Üç yüz kırk beş hasta ve 250 kontrol olmak üzere toplam 595 olgu çalışmaya dahil edildi. Diyabetik olguların yaşı 12,7±4,0 yıl, kontrol grubunun yaşı ise 11,9±4,7 yıldı (p=0,027). Anti-HBS pozitifliği tip 1 diyabetli çocuklarda %51,3 (177 hasta) iken kontrol grubunda %59,4 (149 hasta) ile daha yüksekti (p=0,047). HepA aşısı uygulanan katılımcı sayısı 230 (%38,6) idi. Anti-HAV IgG pozitifliği T1D ve kontrol gruplarında benzerdi (sırasıyla 173 (%50,2) ve 136 (%54,4), p=0,378). HepA aşısı olmayan 365 katılımcıda Anti-HAV IgG pozitifliği %29,4 (n=107) iken, aşı olan 230 çocukta bu oran %90,8 (n=209) idi (p<0,001).

Sonuç: T1D hasta grubunda aşılama sonrası hepA virüsüne karşı yeterli immün yanıt elde edilirken, aşılamaya rağmen hepB virüsüne karşı yetersiz immün yanıt gözlendi. Tanı anında hepA aşısı olmayan bu riskli kronik hasta grubunda Anti-HAV IgG testi yapılarak immun yanıt dikkate alınabilir. Aşılama durumundan bağımsız olarak tüm hastalarda anti-HBS düzeylerinin rutin olarak izlenmesini, bu taramanın kılavuzlarda yer almasını ve antikor yanıtı yetersiz olan hastalara rapel doz aşı uygulanmasını öneriyoruz.

Anahtar kelimeler: Anti-HBS, Anti-HAV IgG, Pediatrik, Tip 1 Diabetes Mellitus.

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INTRODUCTION

Hepatitis B (hepB) is a virus, that is common in the developing world, easily transmitted by sexual, blood and household contact. It can cause cirrhosis and hepatocellular carcinoma (Bond, 1981). HepB virus vaccine was included in the vaccination program for the first time in Turkey in 1998 and 3 doses of vaccination were started to be administered free of charge (Sevda ARSLAN & Seltap GÜLCÜ, 2018). Although protection is reported at varying rates in vaccinated individuals, the antibody level decreases over time after vaccination (Arslanoğlu, Çetin, İşgüven, & Karavuş, 2002; Leonardi et al., 2012; Roznovsky et al., 2010; Altındis et al., 2012). In Turkey, it is not in routine practice to apply a booster dose by measuring the antibody level in the current vaccination scheme.

HLA system is critical for the control of the immune response, since it applies in the mechanisms of immune recognition of all foreign substances that keep in contact with the immune system. Therefore it is likely that individuals expressing specific HLA molecules may respond abnormally to immunization. With this regard, the expression of HLA-DQ2 seems to be associated with a poor antibody production in response to the HBV vaccine. Since more than 90% of diabetic patients expresses one or both DR3/DQ2, DR4/DQ8 haplotypes, this HLA profile could justify by the unresponsiveness to HBV vaccine in diabetic patients.

Hepatitis A (hepA) vaccine has been applied in the routine vaccination program in Turkey since 2012. For this reason, susceptibility to hepA virus continues in the society because routine vaccination is not applied in the group of children older than 11 years of age. Both viruses can have a severe course in diabetes, which is a chronic immune system-based disease. HepA virus can cause acute liver failure, while hepB virus can become chronic and cause severe complications. Our aim in this study is to evaluate the antibody response to hepA and hepB vaccines in the pediatric patient group with type 1 diabetes mellitus (T1D) and compare with healthy children.

MATERIALS AND METHODS

In this cross-sectional study, 345 children diagnosed with T1D and 250 healthy controls followed up in Adana City Training and Research Hospital Pediatric Endocrinology Clinic between 2010 and 2022 were included. The cases were between 3-18 years of age. T1D was diagnosed according to International Society for Pediatric and Adolescent Diabetes (ISPAD) diagnostic criteria (Mayer-Davis et al., 2018). Patients who applied to the Pediatric Endocrinology outpatient clinic for routine examination, were included as the control group. It was confirmed from the vaccination certificates or the verbal approvals of the parents that the vaccination scheme of all participants was completed according to the Ministry of Health vaccination schedule. HepB vaccine was administered at 0, 1 and 6 months, and hepA vaccine at 18 and 24 months. Participants with a history of hepatitis, using additional immunosuppressive drugs or comorbidities were excluded from the study. HepB vaccine protection of the cases was evaluated by measuring anti-HBS level. In order to exclude chronic hepB infection, HBsAg levels were measured. Anti-HBS values >10 IU/mL were considered positive. HepA vaccine protection was evaluated by anti-hepatitis A virus immunoglobulin G (Anti-HAV IgG) level, a cut-off value of >0.99 S/CO was considered positive. Ethics committee approval was obtained from Adana City Training Hospital, date: 19.08.2021, approval number: 1513. The parents of participants were approved the study, and the study was arranged in accordance with the Declaration of Helsinki.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). Chi-square and Fisher's exact tests were used in the comparison of categorical expressions. Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. Independent Student's t-test was used for normally distributed parameters and Mann Whitney U test was used for not normally distributed parameters. Spearman rho correlation test was used to examine the relationship between continuous measurement parameters. Statistical significance level was taken as 0.05 in all tests.

RESULTS

Three hundred and forty-five patients and 250 controls, totally 595 cases were included in the study. Of the cases, 283 (47.6%) were female and 312 (52.4%) were male. The diagnosis age of T1D cases was 8.97±4.1 years and current age was 12.7±4.0 years. The age of the control group was 11.9±4.7 years (p=0.027). While anti-HBS positivity was 51.3% (177 patients) in diabetic children, it was higher with 59.4% (149 patients) in the control group (p=0.047). The number of participants who received hepA vaccine was 230 (38.6%). Anti-HAV IgG positivity was similar in T1D and control groups (173 (50.2%) and 136 (54.4%), respectively, p=0.378). Antibody levels of the cases are given in ***Table-1.***

Table 1. Demographic Data and Antibody Levels

	Patient Group (n=345)	**Control Group (n=250)**	**p**
	n (%)	**n(%)**	
Gender			
Female	164 (47,5)	119 (47,6)	0,988[a]
Male	181 (52,5)	131 (52,4)	
Anti-HBS			
Negative	168 (48,7)	101 (40,6)	0,047*,[a]
Positive	177(51,3)	149 (59,4)	
Anti-HAV IgG			
Negative	172 (49,8)	114 (45,6)	0,378[a]
Positive	173 (50,2)	136 (54,4)	
Hepatitis A vaccination			
No	221 (64,1)	144 (57,6)	0,110[a]
Yes	124 (35,9)	106 (42,4)	
Anti-HBS (Med (Min-Max))	10,5 (0-1000)	15,9 (0-1000)	0,144[b]
Anti HAV-IgG (Med (Min-Max))	1,00 (0,07-18,69)	1,33 (0,09-14,71)	0,191 [b]

* p<0,05, a: Chi-square and Fisher's exact, b: Mann Whitney U test

While there was no difference between the two groups in terms of anti-HBS positivity when evaluated according to gender (p=0.439), anti-HAV IgG positivity was higher in girls than boys [163 patients (57.5%) 144 patients (46.2%) respectively, p=0.012].

There was a weak negative correlation between the age of all participants and their anti-HBS levels (r=-0.110; p=0.008, respectively) and a moderate negative correlation with the anti-HAV IgG value (r=-0.420; p<0.001).

Anti-HAV IgG positivity was 29.4% (n:107) in 365 participants who were born before March 1, 2011 and who did not receive hepA vaccine, while this rate was 90.8% (n:209) in 230 children who were vaccinated (p<0.001).

DISCUSSION

In this study, we showed that the immune response against hepB vaccine is defective in pediatric T1D patients. Anti-HAV IgG positivity was similar in T1D and control groups. In this regard we want to emphasize to monitor Anti-HBS levels in diabetic patients routinely (Wang et al.,2004).

It is known that the possibility of exposure to hepB virus increases in T1D patients due to repeated blood glucose measurement, insulin injections and hospital visits (Schaffzin et al., 2012). Although antibody positivity is found to be 98.7% when the antibody level is examined in the early period after hepB vaccination in diabetic patients, this rate decreases over time (Halota, Muszyńska, & Pawłowska, 2002). Many studies have shown that the efficacy of the vaccine in T1D children and adults is lower than healthy controls (Arslanoğlu et al., 2002; Elrashidy et al., 2013; Fiçicioğlu et al., 1995; Halota et al., 2002; Onal et al., 2016). For this reason, it is important to evaluate the vaccine response in this group who were sensitive to the virus.

T1D is an autoimmune disease involving the cellular and humoral immune systems. Autoreactive CD4+ T cells play a role in the onset of the disease. In this system, some HLA groups are considered to be risky for the development of diabetes. These include both HLA-DQ and HLA-DR (Mikk et al., 2020; Zhou & Jensen, 2013). The immunological response for the hepB vaccine is formed

as a result of molecular mediation of both HLA-DQ and HLA-DR (Martinetti et al., 2000; Wang et al., 2004). HLA-DQ2, DR3, DR4 alleles have been associated with poor vaccine response. This explains the inadequacy of vaccine responses due to these regions that share common alleles with diabetes.

It has been shown that antibody titers become negative at a rate of 15-50% after 5-15 years after the vaccination program in healthy children who received hepB vaccine (C.-Y. Lu et al., 2004). Despite negative antibody titer, it has been shown that there is an amnestic response in memory cells, and therefore routine administration of hepB booster dose is not recommended (Chang et al., 2014; Roznovsky et al., 2010; Schillie et al., 2018). However, in some countries such as Taiwan, where the disease is endemic, it has been shown that 10.1% of patients with negative antibody response to the vaccine do not have an amnestic response and the risk of infection continues (C. Lu et al., 2008). Sivestri et al. showed that the rate of unresponsiveness to the vaccine was found to be 55.2% in 201 type 1 diabetic children, similar to our data, and the amnestic response in this patient group was examined and true vaccine unresponsiveness was found in 10% of the patients (Silvestri, Tromba, Mazzotta, & Costantino, 2019). In terms of screening these children without amnestic response; according to the recommendations of the United States Immunization Practices Advisory Board, it is not recommended to measure antibody titers in children and adolescents whose vaccination program has been completed. In addition, there is no recommendation for routine hepatitis antibody titer screening diabetes diagnosis and treatment guidelines (Craig et al., 2022)We think that this patient group, which is known to be at risk against hepatitis viruses and whose vaccine antibody response is known to be low, is at risk against hepB and that adequate screening is ignored.

In a study from Turkey, 144 T1D patients and 58 control were evaluated. The median anti-HBs levels (14.8 mIU/ml and 37.7 mIU/ml p=0.026), median anti-HAV IgG levels (11 mIU/ml and 19.8 mIU/ml, p <0.001), hepatitis B virus (HBV) seropositive patient rate (%59 and %73.7, p=0,048) and hepatitis A virus (HAV) seropositive patient rate (%27.5 and %44.2, p=0,027) were lower in patients with T1DM comparing to control group (Büyükinan & Kilinç, 2021).

Vaccination against hepA virus, which can cause acute fulminant hepatitis and can lead to emergency liver transplantation in adult patients, has been routinely administered at 18-24 months in our country since year 2012 (Alkan Çeviker, Günal, & Kiliç, 2019). While the seropositivity rate was above 90% in people aged 20 and over before vaccination, this rate decreased in the non-vaccinated group with the date the vaccine was introduced into the routine program. Thus, the age of encountering hepA shifts forward. In our study, it was shown that the vaccine provided an adequate immune response in both groups. However, the seropositivity rate in the unvaccinated group remained at 29.4%. For this reason, we recommend the administration of hepA vaccine in patients who were diagnosed with T1D and born before 2011 but routine hepA antibody measurement was controversy.

CONCLUSION

As a result; in T1D pediatric patient group, while adequate immune response was achieved against hepA virus after vaccination, insufficient immune response was observed against hepB virus despite vaccination. Anti-HAV IgG testing in this risky group of chronic patients who have not been vaccinated with hepA vaccine at the time of diagnosis may be taken into account. In all patients, regardless of vaccination status, we recommend routine monitoring of anti-HBS levels, this screening should be included in the guidelines, and a booster dose of vaccine for patients with inadequate antibody response should be applied.

Author Contributions

Plan, design: A.A; **Material, methods and data collection:** A.A, M.K.Ç; **Data analysis and comments:** A.A, M.K.Ç; **Writing and corrections:** A.A, M.K.Ç.

Conflict of interest

The authors declare that they have no conflict of interest

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