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HLA DQ2 and HLA DQ8 genetic evaluation in children with Type 1 Diabetes Mellitus and Celiac Disease

Aysun Ata[1]*, Özlem Anlaş[2], Didem Gülcü Taşkın[3]

1 Adana City Training and Research Hospital Pediatric Endocrinology, Adana, TR
2 Adana City Training and Research Hospital Pediatric Gastroenterology, Adana, TR
3 Adana City Training and Research Hospital Medical Genetics, Adana, TR

*** Corresponding Author:** Aysun Ata **E-mail:** draysunkaya@gmail.com

ABSTRACT

Objective: Celiac disease (CD) is an autoimmune disease, and other autoimmune diseases co-existence is very high, like type 1 diabetes mellitus (T1DM). Our study aimed to determine the genetic structure of HLADQ2 and HLADQ8 in pediatric patients with T1DM and CD.

Materials and Methods: Our study was conducted retrospectively in patients aged 1-18 years with CD and T1DM, who were followed up in the Pediatric Endocrinology Outpatient Clinic in Adana, Turkey.

Results: A total of 876 patient records with a T1DM diagnosis were reviewed, and the genetic testing of 41 patients with CD and T1DM was evaluated. In 27 of these 41 patients, genetic analysis was performed by the same method and could be evaluated. Of the cases, 12 (44.4%) were female and 15 (55.6%) were male. The mean follow-up duration for the patients was 3.12 ± 1.75 years. The current age of the patients was 12.7± 3.71 years. While 7 (25.9 %) patients were symptomatic, 20 (74.1%) patients were asymptomatic when diagnosed with CD. The highest rates of HLA DQ2 and HLA DQ8 were found in patients with T1DM and CD.

Conclusion: In this study, we investigated, for the first time in our country, the HLA characteristics and clinical findings of a group of pediatric patients with both type 1 diabetes mellitus (T1DM) and celiac disease (CD). The rate of patients with HLA-DQA1* 05-DQB1 * 02-DQB1 *03:02 co-existence (HLA DQ2 and DQ8 co-positivity) was found to be as high as 40.7%, and this carrier was thought to be the riskiest group for T1DM and CD co-existence.

Keywords: Pediatric, celiac disease, type 1 diabetes mellitus, HLA DQ2, and HLA DQ8

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INTRODUCTION

Celiac disease (CD) is an autoimmune, multisystemic, chronic disease of the gastrointestinal system triggered by exposure to gluten and by environmental factors in individuals with HLA-DQ2 and/or HLA-DQ8 genetic structure. HLA-DQ2 is encoded by HLA-DQA1*05:01 and DQB1*02:01 alleles, while HLA-DQ8 is encoded by DQB1*03:02 and DQA1*03:01 alleles. The prevalence of CD is 1% of the population (1) . While immune-genetic predisposition to CD is present in 30 to 40% of the general population, insignificant proportion of them develops the disease at a later stage of life (approximately 3% (2) . There is no doubt that genetic mutations in CD may lead to a predisposition to the disease, but these mutations are not sufficient to diagnose active disease. The absence of genetic mutations is of great value for disease exclusion (3).

It is a well-known fact that some disease groups, such as CD and other autoimmune diseases, coexist. In particular, children with type 1 diabetes mellitus (T1DM) are 6-10 times more likely to develop CD than the general population, although it varies geographically (4). The prevalence of CD in children with T1DM ranges from 1.6% to 16.4% from different populations. In our study, we aimed to investigate the genetic structure of HLADQ2 and HLADQ8 in children diagnosed with T1DM and CD.

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MATERIALS AND METHODS

Our study included patients aged 1-18 who were followed up between 09/18/2017 and 11/30/2022 in the Pediatric Endocrinology Outpatient Clinic of Adana City Training and Research Hospital with CD and T1DM. This retrospective study included patients with CD genetic data in their files. Patients whose diagnosis was not confirmed by a gastroenterologist were excluded from the study. Parameters such as age, sex, age at T1DM diagnosis, age at CD diagnosis, concomitant diseases, current HbA1c level, MARSH evaluation of gastroscopic biopsy, and results of the genetic analysis were recorded and statistically analyzed. Ethics approval was obtained from the Ethics Committee of Adana City Training and Research Hospital, and the study was conducted in accordance with the Helsinki Declaration.

During HLA testing, patients' genomic DNA was extracted from peripheral blood samples using the Qiagen Qiaamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. DNA integrity was checked using the Qubit® 3.0 Fluorometer (Thermo Fisher Scientific, US). HLA-DQA1 and HLA-DQB1 alleles were analyzed using the Genvinset ® HLA Celiac real-time PCR assay. Samples that had both the DQA1*05 and DQB1*02 alleles were considered DQ2 positive. When only the DQA1*05 or DQB1*02 allele was present, these samples were considered half DQ2 positive. Samples that had the DQB1*03:02 allele were considered DQ8 positive.

The data of the patients were analyzed using IBM SPSS version 25.0. While categorical data are expressed in numbers and percentiles, data with continuity are analyzed as mean and standard deviation or minimum and maximum. Our data is descriptive.

RESULTS

The records of 876 patients who were followed up with the diagnosis of T1DM in our hospital's Pediatric Endocrinology Outpatient Clinic were reviewed, and 41 patients were evaluated with T1DM and CD. Genetic analysis of only 27 patients with both diseases was conducted by the same method and could be studied. Of these cases, 12 (44.4%) were female, and 15 (55.6%) were male. While CD was diagnosed without biopsy in 9 (33.3%) patients, the biopsy was performed in other patients. When the biopsies of the patients were evaluated according to the MARSH classification, 2 patients were classified as MARSH 1 (7.4%), 2 patients as MARSH 2 (7.4%), 3 patients as MARSH 3a (14.8%), 9 patients as MARSH 3b (33.3%), and 1 patient as MARSH 3c (3.7%). Three (11.1%) of the patients also had Hashimoto's disease. Two of our patients were diagnosed with concurrent trisomy 21. When T1DM was first diagnosed, the number of patients with high celiac antibody titers was 24. Other three patients were diagnosed with CD at the 11th, 14th, and 21st months of follow-up. The mean age at diagnosis of the patients was 9.6±4.1 years. We had 4 patients (14.8%) diagnosed at less than 5 years of age. The mean follow-up duration for patients was 3.12 ± 1.75 years. The current age of the patients was 12.7 ± 3.71 years. While 7 (25.7%) patients were symptomatic, 20 patients were asymptomatic when they were diagnosed with CD. The highest rates of HLA DQ2 and HLA DQ8 were found in patients with T1DM and CD. The genetic distribution of the patients is shown in Table 1.

Table 1: HLA DQ2 and HLA DQ8 genetic distribution rates of patients with T1DM and CD.

	Frequency	Percent (%)
DQ2 positive	6	22.2
DQ2 and DQ8 positive	11	40.7
DQ8 positive	8	29.6
Half DQ2 positive	1	3.7
Half DQ2 and DQ8 positive	1	3.7
Total	27	100.0

*T1DM:Type 1 diabetes mellitus, CD: Celiac Disease

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DISCUSSION

CD and T1DM are autoimmune diseases that develop from the same genetic background. In both diseases, DQ2 and DQ8 from HLA Class 2 molecules have been recognized as risk factors, and even the DQ2 allele has been included in the diagnostic guidelines for CD (5). This study investigated the HLA characteristics and clinical findings of the pediatric patient group with T1DM and CD for the first time in our country (6). DQ and DR- HLA Class 2 molecules are heterodimeric proteins located as transmembranes. These molecules act as receptors for the treated peptides. HLA DQ2 and DQ8 molecules can bind to gluten-derived peptides and serve these peptides to antigen-presenting cells. This triggers an inflammatory response involving CD4+ T cells.

In the studies conducted, HLA characteristics of the healthy population and autoimmune patients were compared, and it was found that HLA-DQ2 poses a risk, especially for CD, while DQ8 poses a risk for T1DM.

When the studies conducted in patient groups with CD were examined, a study conducted in Slovenia found that 90% of the CD group carried the allele of HLA DQ2 encoded DQA1*05 and DQB1*02 (7). A systematic review examined HLA-DQ genotypes in 4945 CD, and 94.94% were found to be DQB1*02 carriers (8). Here, it can be interpreted that there is no DQ2 allele in only 5.06% of the CD group. In studies examining pediatric patients, when 740 pediatric CD patients were examined, the alleles with the highest risk were HLA-DQB1*02:01 (odds ratio (OR) =10.28) and HLA-DQB1*03:02 (OR=2.24)(9). Investigation of the HLA relationship in T1DM patients has revealed more than 40 predisposing genes (10). Because of changing HLA patterns, the incidence of T1DM also changes across countries. High-risk haplotypes in Mediterranean countries are DRB1∗03:01-DQB1∗03:02 and DRB1∗04:01-DQB1∗03:02. In a study conducted in the Gaziantep region in children with T1DM in our country, DRB1* 03-DQB1 *02 was found to be the riskiest haplotype (11). In a study conducted in the Mediterranean region, the presence of HLA DQ8 was found to be as high as 70% only in patients diagnosed with T1DM (12). In our study, this rate was 74%, demonstrating the HLA characteristic of this geographic region.

In studies examining HLA genetics susceptible to both diseases,

DRB1*03-DQA1*05:01-DQB1*02:01 (DR3-DQ2.5) or

DRB1*04-DQA1*03-DQB1*03:02(DR4-DQ8) are the most common haplotypes (13). -Our study found the rate of patients with HLA-DQA1* 05-DQB1 * 02-DQB1 *03:02 co-existence (HLA DQ2 and DQ8 co-positivity) be as high as 40.7%. This group was considered as the riskiest group for T1DM and CD association. Our study found no patient who did not carry both alleles was found. Other studies have shown that the rate of negative HLA DQ B1*02 carriers in patients with CD and T1DM is 3.65% (14).

HLA class 2 increases the risk of the co-existence of T1DM and CD, and many other genes are also held responsible. However, in studies investigating other genetic predispositions, activating clay immunoglobulin-like receptor (KIR) gene, HLA Class 1 ligands, and combinations have also been found to play an important role in the combination of T1DM and CD (15). It has been found that 2DS5 and 3DS1 of the KIR genes are more prevalent in the population with both diseases (16). KIR genes also play a role in pathogenesis by controlling natural killer cells.

Examining the clinical findings of patients with both diagnoses, recent studies show that age at diagnosis is earlier, and the female gender is considered to be at risk for developing CD in T1DM patients (17). In our study, the age at diagnosis was 9.6 ± 4.1 years, while we had only 4 patients who were diagnosed at an age younger than 5 years. There was no predominance of the female sex among the patients (44.4%). Although female gender is a known risk factor for CD, it was considered that it did not add any additional risk for the combination of both diseases in our study (18). Only 8 patients were found to have symptoms when asked about their symptoms. Seven of them reported nonspecific symptoms, while one patient had diarrheal attacks. CD is generally silent in patients diagnosed with T1DM in childhood. Therefore, patients should be evaluated, especially at the time of diagnosis and with regard to CD in the first two years and up to the fifth year of life. In our patient group, all patients were diagnosed with CD in the first 2 years after the diagnosis of T1DM, similar to the literature. In pediatric patients, T1DM is usually the first diagnosed disease, and the diagnosis of CD is made at an older age. If patients are first diagnosed with CD, T1DM is seen in adulthood (19).

CONCLUSION

In conclusion, we showed that carrying HLA-DQ2; HLA-DQA1*05:01, DQB1 * 02:01, and HLA-DQ8; DQB1*03:02 in children is a risk factor for T1DM and CD. Large patient series studies are needed to identify other HLA loci that also increase susceptibility to these two diseases.

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