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Adolesan Çağındaki Çocuklarda Otoimmün Tiroiditte Parvovirus B19'un Rolü

The Role of Parvovirus-B19 in Autoimmune Thyroiditis in Adolescent Children

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ÖZ

Amaç: Bu çalışmanın amacı adolesan çağındaki otoimmün tiroidit patogenezinde Parvovirus B19'un (PV-B19) tetikleyici rolünü belirlemektir.

Materyal ve Metot: Çalışmaya son 6 ayda Hashimoto tiroiditi tanısı konulan 10-18 yaş arası 35 hasta dahil edildi. Kontrol grubu olarak PV-B19 ile ilişkili akut hastalığı olmayan, fizik muayenesinde guatr olmayan, ailede tiroid hastalığı öyküsü olmayan ve tiroid fonksiyon testleri normal olan 35 sağlıklı gönüllü alındı. Katılımcılardan alınan serum örnekleri PV-B19 IgM ve IgG antikorları ve PV-B19 DNA için test edildi. İstatistiksel analiz SPSS programı kullanılarak yapıldı.

Bulgular: Dört (%11,4) hasta ve 5 (%14,3) kontrolde PV-B19 IgM antikorları pozitif iken, 13 (%37,1) hasta ve 6 (%17,1) kontrolde PV-B19 IgG antikorları mevcuttu. PV-B19 DNA'sı hastaların %11,4'ünde (n:4) ve kontrollerin %14,3'ünde (n:5) saptandı. Antikor ve polimeraz zincir reksiyonu pozitifliği açısından hasta ve kontrol grupları arasında anlamlı fark yoktu. Lojistik regresyon analizinde PV-B19 IgG pozitifliği üzerine serbest tiroksin düzeyi (p:0,021), antitiroid peroksidaz antikor düzeyi (p:0,005) ve istmus kalınlığı (p:0,021) etkili bulundu.

Sonuç: Geçirilmiş PV-B19 enfeksiyonları, Hashimoto tiroiditi patogenezinde tetikleyicilerden biri olabilir.

Anahtar Kelimeler: Adolesan, Hashimoto hastalığı, otoimmün hastalık, parvovirus B19

ABSTRACT

Objective: This study aims to determine the triggering role of parvovirus B19 (PV-B19) in the pathogenesis of autoimmune thyroiditis in adolescence.

Materials and Methods: Thirty-five patients aged 10-18 years who were diagnosed with Hashimoto's thyroiditis in the last 6 months were included in the study. As the control group, 35 healthy volunteers without PV-B19 associated acute disease, no goiter in physical examination, no family history of thyroid disease, and normal thyroid function tests were recruited. Serum samples were tested for PV-B19 IgM and IgG antibodies and PV-B19 DNA. Statistical analysis was performed using the SPSS.

Results: PV-B19 IgM antibodies were positive in 4 (11.4%) patients and 5 (14.3%) controls whereas PV-B19 IgG antibodies were present in 13 (37.1%) patients and 6 (17.1%) controls. PV-B19 DNA was detectable in 11.4% of patients (n:4) and 14.3% of controls (n:5). There was no significant difference between the patient and control groups in terms of antibody and polymerase chain reaction positivity. In logistic regression analysis, free thyroxine level (p:0.021), anti-thyroid peroxidase antibody level (p:0.005), and isthmus thickness (p:0.021) were found to be effective on PV-B19 IgG positivity.

Conclusion: Previous PV-B19 infections may be one of the triggers in the pathogenesis of Hashimoto's thyroiditis.

Keywords: Adolescent, autoimmune diseases, Hashimoto disease, parvovirus B19

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INTRODUCTION

Autoimmune thyroiditis (Hashimoto's thyroiditis, HT) is a thyroid disease characterized by mononuclear cell infiltration in the thyroid gland and autoantibodies against thyroglobulin (Tg) and thyroid peroxidase (TPO), often accompanied by hypothyroidism due to the destruction of thyroid follicles.[1] Autoimmune thyroiditis is the most common cause of acquired hypothyroidism and goiter in children and adolescents.[2]

It is thought to develop as a result of the interaction of genetic, endogenous, and environmental factors. Certain human leukocyte antigen (HLA) haplotypes (HLA-DR4, HLA-DR5) have an increased risk for goiter and thyroiditis. Among environmental factors, high iodine intake, chemicals (such as polyaromatic hydrocarbons), certain drugs (such as lithium, and amiodarone), and viral agents such as human T-cell leukemia virus type-1 (HTLV-1), rubella, Herpes simplex virus (HSV), Epstein–Barr virus (EBV), Hepatitis C virus (HCV), and parvovirus B19 (PV-B19) are held responsible for the development of autoimmune thyroiditis.[2,3]

The clinical course of the disease is variable. Most affected children are clinically euthyroid and asymptomatic; however, thyroid functions may differ from hypothyroidism to hyperthyroidism at the time of diagnosis. Anti-TPO sensitivity is the highest screening test. Increased serum thyroid antibodies are not specific for autoimmune thyroiditis; however, their levels are high in autoimmune thyroiditis. In seronegative patients with overt or latent hypothyroidism, the diagnosis of HT is made by ultrasonography (USG) imaging. A definitive diagnosis is made by thyroid biopsy, biopsy may not always be needed.[2-4]

PV-B19 is a common viral infection agent worldwide. Although it is most common in school-age children (5-15 years), the infection can occur at any age.[5,6] PV-B19 infection has been associated with many autoimmune diseases.. The role of PV-B19 in these diseases is not clear, and its presence may be a coincidence in some cases, while it may be a trigger in some cases.[7,8]

According to studies published in recent years, it has been emphasized that PV-B19 can infect normal thyroid epithelial cells and may play a role in the pathogenesis of autoimmune thyroid diseases.[9] Therefore, in this study, we aimed to evaluate the relationship between PV-B19 infection and autoimmune thyroiditis in two groups of newly diagnosed HT patients and healthy controls.

MATERIALS AND METHODS

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki. The study's protocol was approved by the Istanbul University ethics committee (Date:02.04 2015, decision no: 183), and all study-related anonymized data are available upon reasonable request.

Our study included the patients diagnosed with HT in the last 6 months, who applied to İstanbul University, Department of Pediatrics, General Pediatrics, and Growth, Development and Pediatric Endocrinology Department between August 2015 and August 2016. Serum samples were obtained from 35 patients between 10-18 years of age, who were considered adolescents according to the World Health Organization criteria. Patients with positive thyroid autoantibodies and thyroid dysfunction or with goiter without any other reason or with a morphological examination of the thyroid gland (heterogeneity or pseudonodular appearance) on USG were included in the study. Patients with negative autoantibodies who have primary hypothyroidism or subclinical hypothyroidism for no other reason and who have findings consistent with HT on thyroid USG; patients with autoantibody positivity without thyroid dysfunction or goiter, and patients with morphological changes consistent with HT on thyroid USG without any other reason were also included in the study.

Thirty-five randomly selected healthy children without any acute disease associated with PV-B19 infection, no goiter detected in physical examination, no family history of thyroid disease, and normal thyroid function tests, were recruited as the control group.

All serum samples were analyzed for IgG and IgM antibodies were determined using an enzyme-linked immunosorbent assay (ELISA) (Biotek Instruments Inc., USA). PV-B19 DNA study was performed using the Human Parvovirus B19 kit (cat no: Path-HPVB19, PrimerDesign, UK) and oasig Lyophilised 2x qPZR Mastermix (cat no: oasig-standard-150, PrimerDesign, UK) kits in a Light Cycler 2.0 (Roche Diagnostics GmBH, Germany) real-time PCR system in accordance with the manufacturer's protocol. PV-B19 IgG, IgM, and DNA levels are studied in all samples.

Statistical Analysis: All statistical analyses were performed using IBM SPSS software (version 21.0; IBM Corp., Armonk, NY, USA). Continuous data were expressed as median (range) and categorical data were expressed as number (percentage). Continuous variables were compared using Student's t-test for parametric data and categorical variables were compared using the chi-squared test. Pearson (correlation coefficient: r) correlation tests were used for parametric data, and Spearman (correlation coefficient: rs) correlation tests were used for non-parametric data. Multiple regression and logistic regression analyses were performed. The results

were evaluated with a 95% confidence interval and A P-value of less than 0.05 was considered statistically significant.

RESULTS

Data from 35 patients with HT and 35 healthy children as a control group were analyzed. 80% (n: 28) of patients with HT were female and 20% (n: 7) were male. 68.6% (n: 24) of control group was female and 31.4% (n: 11) was male. The mean patient age was 158.6±26.6 months. The mean age at the time of diagnosis was 155.8±25.9 months. The mean time from the diagnosis of HT was 2.8 ± 1.8 months. The mean age of the control group was 161.9±26.3 months (Table 1).

Table 1. Demographic characteristics of the patient and control groups.

		Patient	Control	p
Age at the time of study (month)	Mean ± SD Median (Min-Max)	158.6 ± 26.6 158 (120-210)	161.9 ± 26.3 160 (120-211)	0.60
Gender n (%)	Female Male	28 (80%) 7 (20%)	24 (68.6%) 11 (31.4%)	0.28
Age at the time of diagnosis (month)	Mean ± SD Median (Min-Max)	155.8 ± 25.9 155 (115-204)	-	
Time between diagnosis and collection of serum samples (month)	Mean ± SD Median (Min-Max)	2.8 ± 1.8 2 (1-6)	-	
Family history of autoimmune thyroiditis n (%)	1º degree relative 2º degree relative Total	4 (11.4%) 3 (8.6%) 7 (20%)	1 (2.9%) - 1 (2.9%)	
Family history of goiter n (%)	1º degree relative 2º degree relative Total	- 2 (5.7%) 2 (5.7%)	-	
Family history of other autoimmune disease n (%)	1º degree relative 2º degree relative Total	1 (2.9%) - 1 (2.9%)	-	

In terms of thyroid function, 10 (28.6%) patients had euthyroidism, 15 (42.9%) subclinical hypothyroidism, 6 (17.1%) hypothyroidism, and 3 (8.6%) hyperthyroidism. Anti-TPO antibodies were detected in 25.7% (n:9) of the patients, anti-TG antibodies in 17.1% (n:6), and both antibodies in 37.1% (n:13). 14.3% of patients had thyroid enlargement in ultrasonography. Thyroid parenchymal heterogeneity was seen in all patients. Pseudonodular appearance was seen in 16 (45.7%) patients (Table 2).

Table 2. Laboratory values of patient and control groups.

		Patient	Control	p
Laboratory				
fT4 (pmol/L)	**Mean ± SD** **Median (Min-Max)**	14.71 ± 6.82 15.8 (0.4-26.3)	15.54 ± 1.86 15.7 (12.2-19.05)	0.49
TSH (mIU/L)	**Mean ± SD** **Median (Min-Max)**	52.71 ± 183 5.23 (0.005-1000)	2.66 ± 0.66 2.67 (1.55-4.01)	0.11
Anti-TPO (IU/ml)	**Mean ± SD** **Median (Min-Max)**	232.3 ± 245.38 136 (5-971)	-	
Anti-TG (IU/ml)	**Mean ± SD** **Median (Min-Max)**	834.64 ± 1368.9 165.9 (0.9-4000)	-	
Thyroid USG				
Total thyroid volume (ml)	**Mean ± SD** **Median (Min-Max)**	17.90 ± 13.02 13.53 (5.29-59.10)	-	
Thyroid right lobe volume (ml)	**Mean ± SD** **Median (Min-Max)**	10.32 ±8.53 7.14 (2.59-37.85)	-	
Thyroid left lobe volume (ml)	**Mean ± SD** **Median (Min-Max)**	8.38 ± 6.19 5.76 (2.7-28.22)	-	
Isthmus thickness (mm)	**Mean ± SD** **Median (Min-Max)**	2.86 ± 2.08 2.5 (0.5-11)	-	
Growth in thyroid volume	**N (%)**	5 (14.3%)		
Heterogeneous appearance	**N (%)**	35 (%100%)	-	
Pseudonodular appearance	**N (%)**	16 (%45.7%%)	-	

fT4: Free thyroxine; TSH: Thyroid stimulating hormone; Anti-TG: Anti- thyroglobulin; Anti-TPO: Anti-thyroid peroxidase; PV-B19: Parvovirus B19.

Table 2. Continue.

PV-B19IgG	**Mean ± SD** **Median (Min-Max)**	0.626 ± 0.758 0.063 (0.032-1.812)		0.359 ± 0.614 0.059 (0.038-1.674)		0.11
PV-B19IgM	**Mean ± SD** **Median (Min-Max)**	0.272 ± 0.529 0.068 (0.044-1.783)		0.286 ± 0.562 0.061 (0.045-1.712)		0.918
		+	-	+	-	
PV-B19 IgG	**N(%)**	13 (37.1%)	22 (62.9%)	6(17.1%)	29(82.9%)	0.061
PV-B19 IgM	**N(%)**	4(11.4%)	31 (88.6%)	5(14.3%)	30(85.7%)	0.726
PV-B19 PCR	**N(%)**	4(11.4%)	31 (88.6%)	5(14.3%)	30(85.7%)	0.726

fT4: Free thyroxine; TSH: Thyroid stimulating hormone; Anti-TG: Anti- thyroglobulin; Anti-TPO: Anti-thyroid peroxidase; PV-B19: Parvovirus B19.

Parvovirus IgM antibodies were positive in 4 (11.4%) patients and 5 (14.3%) controls, while Parvovirus IgG antibodies were present in 13 (37.1%) patients and 6 (17.1%) controls. PV-B19 DNA was detectable in 11.4% of (n:4) patients and 14.3% (n:5) controls (Table 3).

Table 3. The relationship between laboratory findings of the patient group and PV-B19 serology.

	Parvovirus IgG		**Parvovirus IgM**	
	r	**p**	**r**	**p**
TSH	0.009	0.958	-0.98	0.575
fT4	0.166	0.340	0.054	0.757
Anti-TPO	0.434	**0.009**	-0.313	0.067
Anti-TG	0.058	0.741	-0.191	0.272
Thyroid right lobe volume	0.103	0.555	-0.012	0.944
Thyroid left lobe volume	0.093	0.595	0.066	0.705
Thyroid isthmus thickness	-0.162	0.352	0.134	0.443

fT4: Free thyroxine; TSH: Thyroid stimulating hormone; Anti-TG: Anti- thyroglobulin; Anti-TPO: Anti-thyroid peroxidase.

There was no significant difference between the patient and control groups in terms of antibody and PCR positivity. Using multiple linear regression analysis, concentrations of PV-B19 IgG were correlated with free thyroxine (fT4) and anti-TPO antibodies concentrations. In logistic regression analysis, fT4 level, anti-TPO level, and isthmus thickness were found to be effective on PV-B19 IgG positivity (Table 3,4,5).

Table 4. Evaluation of the effect of fT4, anti-TPO level, thyroid right and left lobe volumes on PV-B19 IgG level in HT cases with multiple linear regression analysis.

	Unstandardized Coefficients		**Standardized Coefficients**	**p**	**CI (95%)**
	B	**Standard error**	**Beta**		
fT4	-0.040	0.018	0.359	**0.029**	0.004-0.076
Anti-TPO	0.002	0.000	0.558	**0.001**	0.001-0.003

fT4: Free thyroxine; Anti-TPO: Anti-thyroid peroxidase.

Table 5. Evaluation of variables affecting PV-B19 IgG positivity in HT cases by logistic regression analysis.

	B	**P**	**Odd ratio**	**CI (95%)**
fT4	0.405	**0.021**	1.499	1.063-2.114
Anti-TPO	0.015	**0.005**	1.015	1.005-1.026
Isthmus thickness	-1.428	**0.021**	0.240	0.072-0.803

fT4: Free thyroxine; Anti-TPO: Anti-thyroid peroxidase.

DISCUSSION AND CONCLUSION

Hashimoto's thyroiditis is thought to be a multifactorial disease that develops as a result of the interaction of genetic, endogenous, and environmental factors. Studies on seasonal and geographical distribution and positive serology have shown that infectious agents can trigger HT. In cases with a persistent viral infection, it is thought to trigger autoimmunity through molecular similarity. Especially viral agents such as HTLV-1, enterovirus, rubella, mumps, HSV, and EBV are shown to be associated with HT.[8,10,11]

PV-B19 infection has been associated with many thyroid diseases, including autoimmune thyroiditis, in recent years. The first case of the relationship between PV-B19 and thyroid diseases was reported by Vejlgaard et al.[9] PV-B19 IgG and IgM positivity were shown in a 32-year-old female patient with subacute thyroiditis.[12] However, a direct cause-effect relationship between these two conditions has not been proven. Mori et al.[13] showed that HT developed in a 37-year-old female patient with a history of acute PV-B19 infection one year ago, and detected PV-B19 DNA in the thyroid gland in the fine needle aspiration biopsy. This case shows that chronic PV-B19 infection may be accompanied by a high titer of anti-TPO and anti-TG and there is a cause-effect relationship between autoimmune thyroiditis and persistent infectious agent in the thyroid gland without viremia. Researchers show that persistent PV-B19 infection may play a role in the pathogenesis of HT. In a case-control study performed by Lehmann et al.[14] in the pediatric population, 73 children and adolescents with autoimmune thyroiditis were compared with 73 healthy controls in terms of PV-B19 viremia and serological status. While no significant difference was found between the patient and control groups in terms of PV-B19 serology, PV-B19 viremia was found to be significantly higher in the patient group with HT. In a similar study by Heidari et al.[15], there was a significant positive correlation between PV-B19 IgG and anti-TPO and anti-TG compared with euthyroid controls. Wang et al.[16] investigated the presence of PV-B19 DNA in the pathology preparations of 86 patients and PV-B19 viremia was detected more frequently in Hashimoto's thyroiditis when compared with other thyroid diseases. Gravelsina et al.[17] detected a higher prevalence of the B19V DNA in autoimmune and non-autoimmune thyroid gland diseases than in the control group of individuals whose histories did not show any autoimmune or thyroid diseases. In our study, the relationship between PV-B19 and Hashimoto's thyroiditis was investigated. According to PV-B19 ELISA and PCR results, there was no statistically significant difference between the patient and control groups, but the fact that Parvovirus IgG was positive in %37.1% of HT cases suggests that previous PV-B19 infection may be one of the factors triggering the formation of HT. This finding is consistent with PV-B19 seroprevalence studies conducted in the general population.[5,15] In our study, the anti-TPO level was found to be effective on PV-B19 IgG positivity. These results suggest that previous PV-B19 infection may be one of the factors triggering the formation of HT.

One of the limitations of this study may be that we investigated the presence of DNA only in serum samples and did not include thyroid tissue samples in our study. Tozzoli et al.[18] argued that the presence of antibodies to a virus common in the general population does not prove that this pathogen causes an autoimmune disease. A negative viral serology at the onset of the disease does not exclude the viral hypothesis, since viral triggering may have occurred years ago. Since they can persist in the tissue without systemic manifestations, it is necessary to search for viral agents in the tissues. Although it is known that tissue samples are a valuable material in studies on thyroid diseases, they were not included in the study because of the possible risks due to the invasive procedure. Another limitation of this study was the inclusion of adolescent patients with a diagnosis of Hashimoto's thyroiditis diagnosed within the last 6 months. Therefore, the number of our cases was not sufficient. Another important point to be mentioned in our study was that PV-B19 IgM and DNA levels were positive in 5 control patients. PV-B19 viremia occurs about 5 to 10 days after exposure and usually lasts about 5 days, virus titers peak in the first few days of infection. At this stage, patients may be asymptomatic or present with nonspecific flu-like illness. Five patients in the control group in our study may have asymptomatic Parvovirus infection, and therefore IgM and PCR positivity may be present.

In conclusion, although PV-B19 is theoretically thought to trigger autoimmune thyroid disease, there is insufficient evidence for the role of PV-B19 in the pathophysiology of autoimmune thyroid diseases. Further prospective cohort studies with larger numbers of patients would be beneficial to demonstrate this association.

Ethics Committee Approval: The study was approved by the Istanbul University ethics committee (Date:02.04 2015, decision no: 183).

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept- CD, FO; Supervision- FO, FB; Materials-CD, ZYA; Data Collection and Processing- CD, HB, MOK, AA; Analysis and Interpretation- CD, FB; Writing- CD.

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