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INVESTIGATION OF THE TRIGGERING ROLE OF INFECTIOUS AGENTS IN THE PATHOGENESIS OF AUTOIMMUNE THYROIDITIS IN CHILDREN AND ADOLESCENTS

ÇOCUKLAR VE ERGENLERDE OTOİMMÜN TİROİDİTİN PATOGENEZİNDE ENFEKSİYÖZ ETKENLERİN TETİKLEYİCİ ROLÜNÜN ARAŞTIRILMASI

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Abstract

Objective: Autoimmune thyroiditis (AIT) is a common endocrine disorder in paediatrics. Although genetic and environmental factors contribute to its development, infectious agents have also been considered as triggers. This study examined the potential role of Epstein–Barr virus (EBV), cytomegalovirus (CMV), parvovirus B19, HIV, HCV, and toxoplasma gondii in paediatric AIT.

Material and Methods: Forty-nine patients (aged 1–18 years) who presented to the Paediatric Infectious Diseases and Paediatric Endocrinology outpatient clinics and were diagnosed with autoimmune thyroiditis (AIT) within the previous six months were included in the study. Viral serology was routinely performed during the evaluation for lymphadenopathy in the Paediatric Infectious Diseases clinic. The diagnosis of AIT was based on positive thyroid autoantibodies (anti-TG, anti-TPO, and TSI), with or without thyroid dysfunction, and ultrasound findings suggestive of thyroiditis. Clinical and laboratory data were retrospectively analysed using SPSS version 22.

Results: The median age was 13.1 years (IQR: 4.6). Of the patients, 14.3% (n=7) were male and 85.7% (n=42) were female. Four patients had Graves' disease, and the rest had Hashimoto's thyroiditis. Treatment was required in 53.1% (n=26). Parvovirus IgM was positive in three patients, EBV VCA IgM in four, and both in one. No significant differences in anti-TPO or anti-TG levels were found between

Öz

Amaç: Otoimmün tiroidit (AIT), pediatrik endokrinolojide yaygın görülen bir hastalıktır. Genetik ve çevresel faktörlerin yanı sıra enfeksiyöz ajanların da hastalığın gelişiminde rol oynayabileceği öne sürülmüştür. Bu çalışma, Epstein-Barr virüsü (EBV), sitomegalovirüs (CMV), Parvovirüs B19, HIV, HCV ve Toxoplasma gondii'nin pediatrik AIT'deki potansiyel rolünü incelemektedir.

Gereç ve Yöntemler: Önceki altı ay içinde otoimmün tiroidit (AIT) tanısı almış, Çocuk Endokrinoloji ve Çocuk Enfeksiyon Hastalıkları polikliniklerine başvuran 1–18 yaş aralığındaki 49 hasta çalışmaya dahil edildi. Viral seroloji, Çocuk Enfeksiyon Hastalıkları polikliniğinde lenfadenopati değerlendirmesi sırasında rutin olarak yapılmıştı. AIT tanısı, tiroid fonksiyon bozukluğu olsun ya da olmasın, pozitif tiroid otoantikorları (anti-TG, anti-TPO ve/veya TSI) ve/veya tiroidite işaret eden ultrasonografi bulgularına (heterojenite veya psödonodüler görünüm) dayanılarak konuldu. Klinik ve laboratuvar verileri retrospektif olarak toplanarak SPSS sürüm 22 kullanılarak analiz edildi.

Bulgular: Hastaların medyan yaşı 13,1 yıl (IQR: 4,6) idi. Hastaların %14,3'ü (n=7) erkek, %85,7'si (n=42) kızdı. Dört hastada Graves hastalığı, geri kalanında Hashimoto tiroiditi vardı. Hastaların %53,1'i (n=26) tedavi gerektirdi. Üç hastada Parvovirüs IgM, dört hastada EBV VCA IgM ve bir hastada her ikisi de pozitif bulundu. Seropozitif ve seronegatif hastalar arasında anti-TPO veya anti-TG seviyeleri açısından anlamlı fark saptanmadı. Hiçbir hastada

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the seropositive and seronegative patients. No cases had HIV or HCV, and 97% tested negative for Toxoplasma gondii antibodies.

Conclusion: Parvovirus B19 and EBV may contribute to AIT pathogenesis, but larger studies are needed to confirm these findings.

Keywords Autoimmune thyroiditis · Epstein–Barr virus · parvovirus B19 · cytomegalovirus · toxoplasma gondii · children and adolescents

HIV veya HCV saptanmazken, hastaların %97'si Toxoplasma gondii antikorları açısından negatifti.

Sonuç: Parvovirüs B19 ve EBV, AIT patogenezine katkıda bulunabilir, ancak bu bulguların doğrulanması için daha geniş çaplı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler Otoimmun tiroidit · Epstein-Barr virüs · parvovirus B19 · sitomegalovirüs · toxoplasma gondii · çocuk ve adolesan

INTRODUCTION

Autoimmune thyroid diseases (AITD) result from a dysfunction in the immune system, where T cells primarily mediate an immune response targeting the thyroid. AITD mainly consists of two clinical forms: Graves' disease (GD) and Hashimoto's thyroiditis (HT). Hashimoto's thyroiditis is the most common cause of acquired hypothyroidism and goitre in children and adolescents, whereas the clinical hallmark of GD is thyrotoxicosis (1).

The exact pathogenic mechanisms of AITD are still unknown; however, viral infections are believed to trigger autoimmunity through the mechanism of molecular mimicry. Human T-lymphotropic virus (HTLV-1), enterovirus, rubella, mumps, herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV) are among the viral agents implicated in the pathogenesis of Hashimoto's thyroiditis; however, parvovirus B19 infections are most frequently associated with this condition (2-6).

Additionally, it has been suggested that T. gondii infection might provide protection against autoimmune diseases by extending the hygiene hypothesis from allergic to autoimmune processes, this occurs through the induction of the anti-inflammatory cytokine IL-10, which downregulates the T-cell response to viral infections (7). However, some researchers have also suggested that infection with this protozoon contradicts the idea that it has a protective effect against autoimmune processes (8). In this study, we investigated the direct effect of the most associated viral infections and Toxoplasma gondii infection on the development of autoimmune thyroid disease.

MATERIAL AND METHODS

Forty-nine patients aged 1 to 18 years who presented to the Paediatric Infectious Diseases outpatient clinics between January and December 2024 for the evaluation of lymphadenopathy were included in the study. Viral serology testing and neck ultrasonography were routinely performed during the assessment for lymphadenopathy. During this same period, patients with ultrasound findings suggestive of thyroiditis (heterogeneous echotexture or pseudo-nodular appearance) and/or those with previously incidentally detected thyroid autoantibody positivity and/or thyroid dysfunction were referred to the Paediatric Endocrinology outpatient clinics for further evaluation.

Autoimmune thyroiditis was diagnosed based on the presence of positive thyroid autoantibodies [anti-thyroglobulin (TG), anti-thyroid peroxidase (TPO), or thyroid-stimulating immunoglobulin (TSI)] with or without thyroid dysfunction. Patients who had available viral serology results and were found to have thyroid autoantibody positivity within the previous 6 months were included in the study. Patients with known thyroid autoantibody positivity more than 6 months prior to their initial presentation were excluded. Viral serology and other laboratory parameters were retrospectively collected from medical records. Approval for accessing and analysing retrospective patient data was obtained from the Bioethics Committee of Kartal Lutfi Kirdar City Hospital (Date: 25.12.2024, No: 2024/010.99/11/14), and the study was conducted in accordance with the Declaration of Helsinki.

Thyroid autoantibodies were measured by chemiluminescence immunoassay (CLIA) using the UniCel DxI 800 Access Immunoassay System. The reference range was 0–34 IU/mL for anti-TPO and 0–115 IU/mL for anti-TG. The viral serologies for EBV, CMV, parvovirus B19, human immunodeficiency virus (HIV), and hepatitis C virus (HCV), as well as the serology for Toxoplasma gondii, were performed using enzyme-linked immunosorbent assay (ELISA).

Demographic, anthropometric, clinical, and laboratory findings were obtained retrospectively from the patients' medical records. The pubertal stages were classified according to Tanner. The pubertal status was assessed using the Tanner stages as follows: prepubertal, Tanner 1; pubertal, Tanner 2–4; postpubertal, Tanner 5 (9). Standard deviation scores (SDS) were calculated according to age- and sex-specific national standards (10).

SPSS statistical software, version 22 (IBM SPSS Corp., Armonk, NY, USA), was used for statistical analyses. Data were cleaned and screened for abnormalities. Due to non-normal distribution, continuous variables are presented as medians and interquartile ranges (IQR) to indicate central tendency

and variability, while categorical variables are summarised as counts and percentages. The Mann-Whitney U test was used to compare two independent groups, while the Kruskal-Wallis's test is used to compare three or more independent groups to determine whether there was a statistically significant difference in their distributions. All tests were conducted as two-tailed, with statistical significance established at p≤0.05.

RESULTS

The median age at presentation was 13.1 years (IQR: 4.6, range: 4.2; 17.8). Among the cases, 14.3% (n=7) were male and 85.7% (n=42) were female. The median height- and BMI-SDS in girls were 0.1 (IQR: 1.4, range: −1.9;2.6) and 0.2 (IQR: 1.8, range: −2.6;2.8), respectively. In boys, the median height- and BMI-SDS were 0.2 (IQR: 1.9, range: −1.4;1.6) and 0.3 (IQR: 1.0, range: −1.1;2.7), respectively. BMI SDS was <−2 in 12.2% (n=6) of the patients, between −2 and +2 in 77.6% (n=38), and >+2 in 10.2% (n=5). Of the patients, 16.7 % (n=8) were prepubertal, while 83.3% (n=41) were at Tanner stage 2 or higher.

The median duration from the detection of thyroid abnormalities and positive thyroid autoantibodies to the presentation at the paediatric endocrinology outpatient clinic was 0.07 years (IQR: 0.12, range: 0.01;0.56). Referrals due to thyroid hormone abnormalities accounted for 46.9% (n=23) of the cases, while 53.1% (n=26) of them were referred because of positive thyroid antibodies. The characteristics of patients with autoimmune thyroiditis and the median thyroid hormone and thyroid antibody levels are presented in Tables 1 and 2, respectively. When comparing the anti-TPO and anti-TG levels based on whether the pubertal stage was below stage 2 or at/above stage 2, no statistically significant difference was found in the anti-TPO levels (p=0.299), while there was a significant difference in the anti-TG levels (p=0.045). In the group with a pubertal stage below 2, the median anti-TG level was 1464 (IQR: 1434, range:126-4000), whereas in the group at or above pubertal stage 2, the median anti-TG level was 353 (IQR: 902, range:26-4000). When anti-TPO and anti-TG levels were compared according to BMI-SDS categories (<−2.0, −2 to +2, and >+2), no significant differences were found (p=0.501 and p=0.137, respectively).

Four cases with thyroid hormone abnormalities were ultimately diagnosed with Graves' disease. Notably, in these cases, in addition to positive anti-TPO and anti-TG antibodies, TSI levels were also positive, with measured values of 2.58, 5.24, 3.84 and 7.87 IU/L (normal <0.1 IU/L), respectively. Half of these patients were male (n=2; 50%), half were female (n=2; 50%), and all were postpubertal.

Table 1. Demographic and anthropometric characteristics at referral of 49 patients with autoimmune thyroiditis

Sex	
F n (%)	42 (85.7)
M n(%)	7 (14.3)
Female/male	6:1
Puberty	
≥Tanner stage 2 n (%)	41 (83.3)
<Tanner stage 2 n (%)	8 (16.7)
Age(years)	
>10 years n (%)	40 (81.6)
<10 years n(%)	9 (18.4%)
Sex ratio by age (M/F)	
>10 years n (%)	5 (12.5) / 35 (87.5)
<10 years n(%)	2 (22.2) / 7 (77.8)
Age(years)	13.1 (4.6) (range: 4.2; 17.8)
Female	13.2 (4.4) (range: 4.2; 17.5)
Male	12 (4.8) (range: 5.1; 17.8)
Height- SDS, Median (IQR)	
Female	0.1 (1.4) (range: −1.9;2.6)
Male	0.2 (1.9) (range: −1.4;1.6)
BMI-SDS	
Female	0.2 (1.8) (range: −2.6;2.8)
Male	0.3 (1.0) (range: −1.1;2.7)

F: Female, M: Male, SDS: Standard deviation score, IQR: Interquartile range, BMI: Body mass index

Table 2. Thyroid hormone and thyroid antibody levels of patients at presentation

	Median	IQR	Range
TSH mIU/L	4.05	4.8	0.001-46.5
FT4 ng/dL	1.0	0.33	0.5-4.58
FT3 ng/dL	3.86	0.69	2.63-14.56
Anti-TPO IU/mL (Normal; 0-34)	309	466	5-3390
Anti-TG IU/mL (Normal; 0-115)	436.1	1135.8	28-4000

TSH: thyroid stimulating hormone, FT4: free thyroxine, FT3: free triiodothyronine, Anti-TPO: thyroid peroxidase antibody, Anti TG: thyroglobulin antibody, IQR: IQR: interquartile range

Stage 1 goitre was detected in 10.2% (n=5) of the patients. Heterogeneity of the thyroid parenchyma and a pseudo-nodular appearance were observed in 89.7% (n=44) of the patients, whereas a colloid nodular appearance was identified in 2.2% (n=1) of the patients. The details of the viral serology results of the patients at the presentation are shown in Table 3. Anti-thyroid or thyroid hormone replacement was required

in 53.1% (n=26) of the cases. Among these, 4 patients were started on anti-thyroid treatment, while thyroid hormone treatment was started in 22 patients due to hypothyroidism, and 23 patients remained euthyroid. No statistical difference was observed between those who started the medication and those who did not in terms of anti-TPO and anti-TG levels (p=0.794 and p=0.561, respectively).

Parvovirus IgM positivity was identified in three patients, while EBV VCA IgM positivity was detected in four others. In one patient, both parvovirus IgM and EBV VCA IgM were positive. None of the patients with positive IgM antibodies exhibited any symptoms or clinical findings indicative of the corresponding viral infection. A patient with parvovirus IgM positivity was diagnosed with Graves' disease, while the others were diagnosed with HT. Except for two cases, all individuals (n=6) with positive EBV VCA IgM and parvovirus B19 IgM had medications initiated because of hypothyroidism or Graves' disease. These cases account for 23% of the total patients (n=26) who have started treatment. There was no statistically significant difference between the patients with and without EBV VCA IgM and/or parvovirus IgM positivity in terms of TSH, FT4, FT3, anti-TPO, and anti-TG levels (Table 4).

DISCUSSION

Environmental factors, particularly viral infections, significantly contribute to the onset of autoimmune thyroiditis. In this study, we investigated the viral aetiology in 49 patients who were diagnosed with autoimmune thyroiditis within the past six months.

In this series, IgM antibodies against parvovirus and EBV, which are among the most implicated viral agents in triggering autoimmunity, were detected in eight patients. Moreover, in one patient, both parvovirus and EBV IgM were detected.

Table 3. Viral serology results of the patients at the presentation

	Girls (n=42)		Boys (n=7)		Total (n=49)	
	Positive n (%)	Negative n (%)	Positive n (%)	Negative n (%)	Positive n (%)	Negative n (%)
EBV VCA IgM	4 (9.5)	38 (90.5)	1 (14.2)	6 (85.7)	5 (10.2)	44 (89.8)
EBV VCA IgG	30 (71.4)	12 (28.6)	5 (71.4)	2 (28.6)	35 (71.4)	14 (28.6)
Parvovirus B19 IgM	2 (4.7)	40 (95.2)	2 (28.6)	5 (71.4)	4 (8.2)	44 (89.8)
Parvovirus B19 IgG	21 (50)	21 (50)	1 (14.3)	6 (85.7)	22 (44.9)	27 (55.1)
CMV IgM	-	42 (100)	-	7 (100)	-	49 (100)
CMV IgG	32 (76.2)	10 (23.8)	7 (100)	-	39 (79.6)	10 (20.4)
Toxoplasma IgM	-	32 (100)	-	4 (100)	-	36 (100)
Toxoplasma IgG	-	32 (100)	1 (25)	3 (75)	1 (3)	35 (97.2)
Anti HIV	-	42 (100)	-	7 (100)	-	49 (100)
Anti HCV	-	42 (100)	-	7 (100)	-	49 (100)

EBV: Epstein–Barr virus, VCA: Virus capsid antigen, Ig: Immunoglobulin, CMV: Cytomegalovirus, HIV: Human immunodeficiency virüs, HCV: Hepatitis C virus

Table 4. Comparison between the group with parvovirus IgM and EBV VCA IgM positivity and the group without it

	EBV VCA Ig M Parvovirus B19 IgM positivity (n=8) Median (IQR) (Range)	EBV VCA Ig M Parvovirus B19 M negativity (n=41) Median (IQR) (Range)	p
TSH mIU/L	5.88 (7.49)	3.89 (4.73)	
	(0.36;46.5)	(0.001;25)	0.561
FT4 ng/dL	1.1 (0.33)	0.99 (0.33)	
	(0.8;1.85)	(0.5;4.58)	0.372
FT3 ng/dL	3.78 (0.69)	3.86 (0.66)	
	(3.37;4.67)	(2.63;14.6)	0.810
Anti-TPO IU/mL	358.5 (476)	309 (533)	
(Range; 0-34)	(10.8;1441)	(5.0;3370)	0.801
Anti-TG IU/mL	200.5 (229.9)	575 (1245.8)	
(Range; 0-115)	(126;1539)	(26;4000)	0.282

Ig: Immunoglobulin, EBV: Epstein-Barr Virus, VCA: Virus capsid antigen, TSH: Thyroid stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, Anti-TPO: Thyroid peroxidase antibody, Anti TG: Thyroglobulin antibody, IQR: IQR: Interquartile range

Autoimmune thyroid diseases are known to predominantly affect females, with female-to-male (F:M) ratios ranging from 20:1 to 4:1 in chronic autoimmune thyroiditis and from 9:1 to 4:1 in Graves' disease (11). Findings from animal models indicate that sex differences in the autoimmune response are primarily driven by sex hormones or chromosomal factors, such as skewed X-chromosome inactivation (12, 13). In a study examining adolescents diagnosed with autoimmune thyroiditis, the F/M ratio was reported as 4.2:1 (14). In another study from Türkiye, which included 162 adolescents aged between 4.4 and 16.5 years with HT, the F/M ratio was reported as 6.4:1 (15). In our cohort, when considering total autoimmune thyroiditis, the F/M ratio was 6:1. When subdivided into Hashimoto's thyroiditis and Graves' disease, the ratios were 8:1 and 1:1, respectively. De Vries et al. speculated that the increase in oestrogen levels during puberty in boys might contribute to the higher prevalence of AIT in the pubertal group (14). However, the fact that the F/M ratio of Graves' disease in our study is close to each other may be related to the small sample size included in the study at a cross-sectional period.

In addition to explanations related to sex hormones or chromosomal factors, viral infections may also trigger autoimmune thyroiditis. For instance, following a confirmed parvovirus B19 infection, the detection of parvovirus B19 DNA in the thyroid tissue has been reported to indicate a potential aetiological role in HT (6). Durak et al. compared 35 patients diagnosed with HT in the past six months with 35 healthy controls and found no statistically significant difference in the PV-B19 IgM and parvovirus DNA results. However, the authors concluded that the higher prevalence of parvovirus IgG positivity in patients with HT (37.1%) compared with the control group (17.1%) suggests that a past PV-B19 infection may be one of the factors triggering the development of HT (16). In our series, we detected PV-B19 IgM positivity at 8.2% and IgG positivity at 44.9%. Although we did not compare antibody levels with healthy controls, the lower IgM positivity rate and higher IgG positivity rate may be related to the larger size of our cohort.

Moreover, it has also been reported that cases may present not only with Hashimoto's thyroiditis but also with Graves' disease (17). Seishima et al. reported a case of Parvovirus B19 viremia in a 31-year-old patient diagnosed with Graves' disease, presenting with high FT4 and FT3 levels, elevated TSH-stimulating receptor antibody, and suppressed TSH levels, with detectable Parvovirus B19 DNA. In this case report, although the authors were unable to detect parvovirus DNA through thyroid biopsy, they concluded that parvovirus viremia was the cause of the clinical presentation based on the detection of DNA in the serum along with antibody findings (17). In our series, four patients were diagnosed with Graves' disease, and among these patients, parvovirus IgM antibody positivity was detected in only one case. However, we were unable to measure parvovirus B19 DNA in either the serum or a thyroid gland biopsy.

Janogeva et al. demonstrated the presence of EBV in thyroid tissues affected by autoimmune thyroiditis. The prevalence of EBV nuclear RNA detection was 80.7% in patients with Hashimoto's thyroiditis and 62.5% in those with Graves' disease (18). Thomas et al. compared 34 paediatric patients with autoimmune thyroid disease (AITD) to 31 healthy controls. The percentage of EBV IgG-positive children was significantly higher in the AITD group than in the control group. Additionally, EBV IgM positivity was detected in two patients from each group, and no statistically significant differences were observed in the percentage of EBV IgM-positive children between the AITD patients and the controls (19). In our cohort, the EBV VCA IgM positivity was 10.2% (n=5), while the VCA IgG positivity was 71.4% (n=35). All patients in our series with EBV VCA IgM positivity were diagnosed with Hashimoto's thyroiditis, whereas none were diagnosed with Graves' disease. There was no statistically significant difference in anti-TPO and anti-TG levels when comparing individuals with EBV VCA IgM and Parvovirus B19 IgM positivity to those who were negative. However, 75% of cases with parvovirus or EBV VCA IgM positivity required L-thyroxin or antithyroid treatment. Despite the small cohort size, our results indicate that acute viral infections lead to thyroid dysfunction.

Khoury et al. demonstrated that CMV infection induces HLA-DR expression on thyroid follicular cells in primary thyroid cell cultures (20). Thomas et al. demonstrated no CMV IgM positivity. Additionally, they did not find any statistically significant differences in the prevalence of CMV IgG between children with AITD and the control group (19). In our study, although we did not observe any patients with CMV IgM positivity, most patients (79.6%) were positive for CMV IgG.

Although anti- Toxoplasma gondii antibodies have been linked to autoimmune thyroid diseases (21), Alvarado-Esquivel et al. found a negative correlation between the infection and thyroid dysfunction, including hypothyroidism, in their study (22). Consistent with this study, 73.5% of the cases (n=36) were tested for the possibility of Toxoplasma infection, and 97.2% (n=35) of them were negative for Toxoplasma IgG. These findings support a weak association between autoimmune thyroiditis and Toxoplasma infection. However, missing Toxoplasma gondii antibody data in 13 of 49 patients represented a limitation of our study.

HCV can infect human primary thyrocytes as they express HCV cell surface receptors (23). However, despite the demonstrated association between HCV and AITD, anti-HCV was not detected in any of the patients in our cohort. Additionally, the serology of none of the patients in our series was positive for HIV.

CONCLUSION

Our study has demonstrated that agents such as HIV, HCV, or Toxoplasma gondii are not causative factors in the pathogenesis of autoimmune thyroid disease in the paediatric population. Our findings indicate that viral agents, including parvovirus B19 and EBV, could play a critical etiopathogenic role in autoimmune thyroid disease. However, the absence of a healthy control group limited the ability to establish a clear association. Consequently, our study has left more questions than we initially aimed to address, so further studies are required to uncover the underlying mechanisms.

Ethics Committee Approval	Ethics committee approval was received for this study from the ethics committee of Bioethics Committee of Kartal Lutfi Kirdar City Hospital (Date: 25.12.2024, No: 010.99/11/14).
Informed Consent	Due to the retrospective design of the study, informed consent was not taken.
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of Study- E.K.Ö., C.Ç., A.K.; Data Acquisition- E.K.Ö., C.Ç., A.K.; Data Analysis/Interpretation – E.K.Ö.; Drafting Manuscript- E.K.Ö.; Critical Revision of Manuscript- C.Ç., A.K., Y.A.; Final Approval and Accountability- E.K.Ö., C.Ç., A.K., Y.A.; Technical or Material Support- E.K.Ö., C.Ç., A.K., Y.A.; Supervision- E.K.Ö., C.Ç., A.K., Y.A.
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