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Coexistence of Autoimmune and Allergic Diseases with Autoimmune Thyroid Diseases

Otoimmün Tiroid Hastalıklarıyla Birlikte Seyreden Otoimmün ve Allerjik Hastalıklar

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Abstract

Background: Sometimes, the patients with autoimmune thyroiditis show certain symptoms despite having serum thyroid hormone levels within the desired range. In addition, the dose of levothyroxine replacement may vary in the patients with hypothyroidism. These factors directly influence clinical practices and may, to some extent, be associated with other immunological/allergic diseases that accompany autoimmune thyroid diseases (ATDs).

Purpose: To document the other autoimmune/allergic disorders in patients during follow-up for ATDs.

Materials and Methods: During the study period, 274 patients diagnosed with, and/or at follow-up for Hashimoto's thyroiditis (HT), and 53 with Graves' disease (GD) were included in the study. All the patients were examined and were subjected to further investigations when the presence of other autoimmune/allergic diseases was suspected.

Results: A total of 65 patients with HT (23.8%) and seven patients with GD (13.2%) had at least one additional clinical autoimmune/allergic disorder. Twenty-eight (10.2%) patients with HT had gastrointestinal disorders (chronic atrophic gastritis and celiac disease), 19 (6.6%) had allergies (asthma, chronic urticaria, and rhinosinusitis), 12 (4.4%) had rheumatological disorders (rheumatoid arthritis), 10 (3.7%) had skin problems (vitiligo and psoriasis), four (1.5%) had endocrinological disorders (hypoparathyroidism, type–1 diabetes mellitus, and hypophysitis), one (0.4%) had hematological disease (idiopathic thrombocytopenic purpura), and one (0.4%) had renal disorder (crescentic glomerulonephritis). The prevalence patterns were similar in the patients with GD. In addition, 50 (18.2%) patients with HT and one (1.9%) with GD were observed to have vitamin B12 deficient-anemia (p=0.001). Furthermore, 28 (10.2%) patients with HT and one (1.9%) with GD had dimorphic anemia (both vitamin B12 and iron deficiencies).

Discussion: The patients with ATDs are prone to additional autoimmune/allergic diseases, and it can be said that the patients with autoimmune thyroid diseases sometimes have more than just thyroid disease. The most involved organ system in both HT and GD is the gastrointestinal tract. This involvement probably plays a role in the exacerbation of some symptoms by causing anemia resulting from a deficiency of both vitamin B12 and iron, especially in patients with HT.

Keywords: Hashimoto's thyroiditis; Graves' disease, allergic diseases, chronic atrophic gastritis, autoimmune disorders, vitamin B12 deficiency

Özet

Giriş: Bazen serum tiroid hormon düzeyleri normal aralıkta olsa da otoimmün tiroiditli hastalar semptomatik olabilirler. Diğer yandan, hipotiroidi hastalarında levotiroksin replasman dozu değişkenlik gösterebilir. Klinik yaklaşımı değiştiren bu faktörler bir miktar otoimmün tiroid hastalığına(OTH) eşlik eden diğer immünolojik/alerjik hastalıklarla ilişkili olabilir.

Amaç: OTH için takipteki hastalardaki diğer otoimmün/ alerjik hastalıkları araştırmak

Gereç ve Yöntemler: Çalışma boyunca tanı konulan ya da takip altındaki 274 Hashimoto Tiroiditi (HT) ve 53 Graves' hastalığı (GH) hastası çalışmaya dahil edildi. Tüm hastalardan anamnez alınıp hastalar muayene edildikten sonra otoimmün /allerjik hastalıklar için şüphede olunanlara ek tetkik yapıldı.

Bulgular: 65 (23.8%) HT hastası ve 7 (13.2%) GD hastasının ek olarak en az bir klinik otoimmün/allerjik hastalığı mevcuttu. HT hastalarında hastalıkların dağılımları: 28 (10.2%) gastrointestinal (kronik atrofik gastrit, çölyak hastalığı, vb), 19 (6.6%) allerjik (astım, kronik ürtiker, rinosinüzit), 12 (4.4%) romatolojik (romatoid artrit,vb), 10 (3.7%) cilt (vitiligo, psöriazis, vb), 4(1.5%) endokrinolojik (hipoparatiroidi, tip1 diabetes mellitus, hipofizit), 1(0.4%) hematolojik (idiopatik trombositopenik purpura), 1(0.4%) renal (kresenterik glomerulonefrit) şeklindeydi. GD grubunda bu dağılım benzerdi. Ek olarak, 50(18.2%) HT hastasında ve 1(1.9%) GD hastasında vitamin B12 eksikliği anemisi mevcuttu (p=0.001). 28 (10.2%) HT ve 1 (1.9%) GD hastasında dimorfik (vitamin B12 ve demir eksikliği birlikte) anemi mevcuttu.

Tartışma: OTH hastaları ek otoimmün/allerjik hastalıklara yatkındırlar ve söylenebilir ki otoimmün nedenli tiroid hastalığı olanlarda sadece tiroid hastalığı yoktur. Her iki tip OTH'nda da en çok tutulan organ sistemi gastrointestinal sistemdir. Muhtemelen bu tutulum özellikle HT hastalarında hem vitamin B12 hem demir eksikliğine neden olup anemiye yol açarak bazı semptomların artışına sebep olmaktadır.

Anahtar kelimeler: Hashimoto tiroiditi, Graves' hastalığı, allerjik hastalıklar, kronik atrofik gastrit, otoimmün hastalıklar, vitamin B12 eksikliği

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Introduction

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are two major forms of autoimmune thyroid diseases. Hashimoto's thyroiditis is the most common cause of hypothyroidism, whereas GD is the leading cause of hyperthyroidism in young and middle-aged women (1, 2). In clinical practice, these patients usually have a greater variety and number of complaints than patients with other thyroid disorders (3). The symptoms, which appear to be independent of thyroid hormone levels in patients with HT, become more pronounced with changes in hormone levels in patients with GD (4, 5). On the other hand, inadequate thyroid hormone replacement remains a problem in the patients with hypothyroidism, who are on levothyroxine replacement, despite frequent monitoring and dose adjustments (6). Furthermore, the levothyroxine replacement dose varies depending on whether the thyroid disease is autoimmune or due to some other cause (7).

These observations in clinical practice have led to the investigation of factors associated with other autoimmune diseases, which may contribute to such variations. For example, HT patients with parietal-cell antibodies have been found to require higher replacement doses of levothyroxine. The presence of anemia indicates undiagnosed atrophic gastritis (8), and hence the measurement of serum parietal-cell antibodies has been recommended in patients with an unexplained high requirement of levothyroxine (9). The atypical celiac disease also increases the requirement of thyroid hormone replacement (10).

Apart from these, it is believed that a patient with an autoimmune disease has a tendency to develop other forms of autoimmune or allergic diseases (11). Autoimmune disorders also have a tendency to appear in one family as several cases or in a single patient as multiple types. The routes of induction, pathogenesis, and treatment modalities may be influenced by many of these factors (12). As in most of the autoimmune diseases, the risk of development of autoimmune thyroiditis is determined by genetic and environmental factors. The HLA-DR polymorphisms such as HLA-DR3, -DR4, and -DR5 in Caucasians; HLA-B8, cytotoxic T-lymphocyte antigen (CTLA–4), CD40, protein tyrosine phosphatase–22 (PTPN22), thyroglobulin, and thyroid-stimulating hormone receptor (TSHR) gene polymorphisms have been observed to be associated with autoimmune thyroid diseases (13). Other autoimmune diseases are also observed to be associated with genetic factors; this provides insight into the relationship between autoimmune thyroid diseases and other autoimmune diseases such as type 1A diabetes mellitus, Addison's disease, pernicious anemia, vitiligo, rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome. Each of these disorders can be divided into many stages, beginning with genetic susceptibility, environmental triggers, active autoimmunity, and finally metabolic derangements with overt symptoms of disease (14).

The aim of the present study was to document the additional autoimmune/allergic disorders in Turkish patients at follow-up for autoimmune thyroid diseases. Presently, no large-scale trials describing the cost-benefit ratio of auto-antibody screening for evaluation of autoimmune conditions exist, and hence clinicians are advised to use individual judgment combined with improved awareness to identify the ideal subjects (15). Therefore, we screened patients with symptoms which could not be explained by the current thyroid function status for potential accompanying autoimmune/allergic diseases.

Subjects and Methods

This was a descriptive study. All patients diagnosed with autoimmune thyroiditis (AIT): HT or GD, who attended the Thyroid Diseases Clinic at Ankara University's Ibn-i Sina Hospital between November 2008 and April 2009 and who were older than 18 years, were offered to be enrolled in the study. The study was approved by the Local Clinical Research Ethics Committee and it adheres to the principles outlined in the Declaration of Helsinki. A written consent was obtained by each patient enrolled. All subjects were systemically questioned for each symptom that could be related to incorrectly functioning body systems. The subjects who reported having symptoms unexplainable with the current thyroid disease status were screened for potential additional autoimmune/allergic disease(s). The diagnosis of other autoimmune diseases was made by a specialist in the related department, following the criteria for each disease described below.

Each patient was asked for possible symptoms of the autoimmune diseases being screened. The symptoms reported by the patient directed the clinician to examine specific disease(s). For example, if the patient had arthritis, the clinician checked for Rheumatoid Arthritis, while if xerostomia was reported during systematic questioning, Sjogren's syndrome was investigated. Some additional recommended laboratory tests were also performed to facilitate the accurate diagnosis. Specifically, when anemia associated with deficiency of iron or vitamin B12 was encountered, a gastroduodenoscopy was performed. The diagnostic criteria used to confirm the coexisting autoimmune or allergic diseases and the laboratory tools implemented to support the findings are listed in Table 1 (16–39). For example, the level of anti-transglutaminase Ig-A antibody was measured to confirm celiac disease, and antibody positive patients were subjected to duodenal biopsy (as described in supportive laboratory methods in Table 1).

Definitions

Iron deficiency anemia: low serum ferritin, red cell microcytosis or hypochromia in the absence of chronic disease or hemoglobinopathies

Vitamin B12 deficiency anemia: low cobalamin, macrocytic anemia or macrocytosis with oval macrocytes or hyper-segmented neutrophils or pancytopenia

Dimorphic anemia: low serum cobalamin and ferritin levels with anemia

Hashimoto's thyroiditis: serologically increased levels of anti-TPO (anti-thyroid peroxidase) and/or anti-Tg (anti-thyroglobulin), along with diffuse hypo-echogenicity, heterogeneity, and pseudo-nodules on ultrasonography.

Graves' disease: diffuse thyromegaly associated with heterogeneity on ultrasonography, and the increased levels of thyroid stimulating hormone receptor antibody (Trab) in serum.

Table 1. Diagnostic criteria that were employed to diagnose coexisting autoimmune or allergic diseases, and the laboratory methods that supported these diagnoses.

Autoimmune or allergic disease	Diagnostic criteria	Supportive laboratory methods
Chronic atrophic gastritis	Atrophy of the corpus and fundus, and the presence of circulating autoantibodies to the parietal cell (PCA) and their secretory product, intrinsic factor (AIF) (16)	Gastric corpus and fundus biopsy
Celiac disease	Working Group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition (17)	anti-tTG (anti-tissue transglutaminase) IgA, duodenum biopsy
Autoimmune pancreatitis	Diagnostic criteria derived from the combination of HISORt (histology, imaging, serology, other organ involvement, and its response to steroid therapy) (18)	CT (Computed Tomography) and biopsy of pancreas
Ulcerative colitis	Second European evidence-based consensus on the diagnosis and management of ulcerative colitis (19)	Colonoscopy, preferably with ileoscopy, and segmental biopsies including the rectum
Primary biliary cirrhosis	Fatigue, pruritus, cholestasis, elevated serum AMA (antimitochondrial antibody), percutaneous liver biopsy findings (20)	AST, ALT, ALP, GGT, direct/indirect bilirubin, serum AMA
Asthma	National Asthma Education and Prevention Program 2007 report (Expert Panel Report 3 [EPR–3] (21)	Spirometry
Chronic urticaria	The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. (22)	Lesional skin biopsy
Allergic rhinosinusitis	The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (23)	Nasendoscopy
Rheumatoid arthritis	The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis (24)	Radiography of the hand including the wrist, RF (Rheumatoid Factor)
Systemic lupus erythematosus	1982 ACR (American College of Rheumatology) revised criteria (25)	Complete Blood Count, serum creatinine, 24 h urine protein, Antinuclear antibody, anti-Double stranded DNA antibody
Still disease	Yamaguchi criteria (26)	CBC, AST, ALT, ANA, RF
Sjögren syndrome	Revised version of the European criteria proposed by the American-European Consensus Group (27)	Schirmer's test, saliva test, Antibodies to Ro (SSA) and La (SSB) antigens, salivary gland biopsy
Behçet's disease	International Study Group for Behçet's Disease (28)	Pathergy test
Ankylosing spondylitis	Modified New York Criteria (29)	Sacroiliac radiography
Sarcoidosis	The noncaseating granulomatous inflammation in the respiratory tract, eye, skin, liver, spleen, heart, nervous system or musculoskeletal organs (30)	Biopsy of the involved organ
Mixed connective tissue disease	Alarcon-Segovia classification (31)	Cold water test, anti-RNP (anti-ribonucleoprotein)
Vitiligo	Consensus report of the Vitiligo European Task Force (32)	Wood's lamp examination
Psoriasis	Lesions exhibiting erythema, induration, and scaling, skin biopsy findings (33)	Histopathology
Idiopathic pruritus	European Guideline on Chronic Pruritus (34)	CBC, ESR, creatinine, alkaline phosphatase, liver enzymes, bilirubin, TSH, glucose, serum iron, ferritin, hepatitis serology, cholesterol triglycerides
Total alopecia	Complete non-scarring loss of scalp hair	
Hypoparathyroidism	Hypoparathyroidism not occurring after a surgical procedure or any other well-defined cause (35)	Serum PTH, Calcium, Phosphorus
Type–1 diabetes mellitus	Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (36)	Two separate measurements of plasma glucose, plasma C-peptid, insulin, anti-glutamic acid decarboxylase antibody
Hypophysitis	Compression symptoms (a headache, visual impairment), hypopituitarism, diabetes insipidus or hyperprolactinemia (37)	Magnetic resonance imaging
Immune thrombocytopenia	American Society of Hematology Clinical Practice Guideline (38)	CBC, Peripheral blood smear
Crescentic glomerulonephritis	Edema, hypertension and gross hematuria, and evidence of acute renal failure (39)	Renal biopsy

Table 2. Some characteristics and comparison of the patients with autoimmune thyroid disorders.

	Hashimoto thyroiditis (n=274)	Graves' Disease (n=53)	p-value
Age (years)	45.6 ±12.2	46.3 ±12.4	NS
Gender, male (n,%)	21 (7.7)	17 (32.1)	< .001
Age at diagnosis	40.0 ±12.2	43.7 ±11.5	NS
TSH, at diagnosis (μIU/mL)	6.8 (2.4–11.5)	0.02 (0.01–0.04)	<.001
Anti-tpo, at diagnosis (0–9 IU/mL)	253 (79–968)	153 (25–652)	.025
Anti-tg, at diagnosis (0–4 IU/mL)	102 (25–418)	18 (2–76)	< .001
Anti-tpo, current (0–9 IU/mL)	175 (39–426)	300 (46–834)	NS
Anti-tg, current (0–4 IU/mL)	51 (10–223)	15 (1–93)	.032
Vitamin B12 (pg/mL)	294 (214–431)	223 (161–371)	.022
Ferritin (ng/mL)	16 (7–35)	32 (12–71)	NS
Vitamin B12 deficiency, n (%)	50 (18.2)	1 (1.9)	.001
Iron deficiency, n (%)	58 (21.2)	4 (7.5)	.021
Both deficiencies	28 (10.2)	1 (1.9)	.002

*Vitamin B12 deficiency was considered if the patient was on vitamin B12 replacement, or if the vitamin B12 levels were <200 pg/mL

*İron deficiency was considered if the patient was on iron replacement, or if they had anemia with ferritin levels <30 ng/mL.

Hormone assays

Thyroid-specific antibodies (anti-TPO and anti-Tg) were measured by an electrochemiluminescence method (ECLIA) (Elecsys 2010, Roche Diagnostics, Indianapolis, USA). The normal ranges were 0–34 IU/mL and 0–9 IU/mL for anti-Tg and anti-TPO, respectively. Thyroid receptor antibody(Trab) was measured by a radioreceptor assay (Radim Diagnostics, Pomezia, Italy). The normal level (negative) was <9 IU/L, while 9–14 IU/L was borderline and >14 IU/L was positive. TSH (Thyrotropin) was measured by ECLIA Immulite 2000 (Diagnostic Products Corp, Los Angeles, CA, USA).

Statistical analysis

The normally distributed continuous variables were expressed as the mean and standard deviation (mean ±SD), and were compared using Student's t-test or one-way ANOVA. Non-normally distributed continuous variables were expressed as median and interquartile ranges 25 and 75 [median (IQR 25-IQR 75)], and were compared using the Mann-Whitney U test or Kruskal-Wallis test. When performing correlation and regression analysis, non-normally distributed continuous variables were log-transformed. The evaluation of normality was performed with the Kolmogorov-Smirnov test. The categorical variables were compared using Pearson's chi-squared or Fisher's exact test. The p values below 0.05 were considered to be statistically significant. The software SPSS v.17.0 (SPSS, Chicago, IL) was used for all statistical calculations and graphical presentation.

Results

Although 338 patients with AIT were initially chosen for participation in the study, some patients opted out before giving their consent. Thus, a total of 327 patients (289 female) with autoimmune disorders (274 with HI and 53 with GD) were admitted and included in the study. The median disease duration from the time of diagnosis was four years (2–8 years) in case of HT, and 0.5 years (0–4 years) in case of GD (p<.001). The prevalence of HT in all the studied female patients was 87.5% (n=253), whereas in males it was 55.3% (n=21) (p< 0.001). Overall, 65 (23.7%) patients with HT (48 with additional autoimmune diseases and 19 with allergic diseases, of which two had both additional autoimmune and allergic diseases), and seven patients with GD (five of which had additional autoimmune diseases and two had allergic-based diseases) were found to have at least one additional autoimmune/allergic disease(s). The details of co-existing additional autoimmune/allergic diseases are given in Tables 2 and 3. The most prevalent additional autoimmune diseases were related to the gastrointestinal tract,

Table 3. The distribution of the coexisting autoimmune and allergic-based diseases in patients with Hashimoto's thyroiditis and Graves' disease.

	Hashimoto thyroiditis (n=274)	Graves' Disease (n=53)	p-value
Gastrointestinal*	28 (10.2)	2 (3.8)	NS
Chronic atrophic gastritis	21 (7.7)	1 (1.9)	NS
Celiac disease	7 (2.6)	0	NS
Autoimmune pancreatitis	1 (0.4)	0	NS
Ulcerative colitis	0	1 (1.9)	NS
Primary biliary cirrhosis	1 (0.4)	0	NS
Allergic	19 (6.9)	2 (3.8)	NS
Asthma	13 (4.7)	0	NS
Chronic urticarial	2 (0.7)	1 (1.9)	NS
Rhinosinusitis	5 (1.8)	1 (1.9)	NS
Rheumatological	11 (4.0)	0	NS
Rheumatoid arthritis	2 (0.7)	0	NS
Systemic lupus erythematosus	1 (0.4)	0	NS
Still disease	1 (0.4)	0	NS
Sjögren syndrome	2 (0.7)	0	NS
Behçet's disease	1 (0.4)	0	NS
Ankylosing spondylitis	1 (0.4)	0	NS
Mixed connective tissue disease	3 (1.1)	0	NS
Skin**	9 (3.3)	2 (3.8)	NS
Vitiligo	4 (1.5)	2 (3.8)	NS
Psoriasis	3 (1.1)	0	NS
Idiopathic pruritus	3 (1.1)	0	NS
Total alopecia	1 (0.4)	0	NS
Endocrinological	4 (1.5)	0	NS
Idiopathic hypoparathyroidism	2 (0.7)	0	NS
Type–1 diabetes mellitus	1 (0.4)	0	NS
Hypophysitis	1 (0.4)	0	NS
Others			
Immune thrombocytopenia	1 (0.4)	1 (1.9)	NS
Crescentic glomerulonephritis	1 (0.4)	0	NS
Sarcoidosis	1 (0.4)	1 (1.9)	NS

* Two patients had more than one additional autoimmunity related gastrointestinal diseases.

**Two patients had more than one additional autoimmunity related skin diseases.

Table 4. Some characteristics of the patients with Hashimoto's thyroiditis with and without additional autoimmune gastroenterologic involvements.

	With accompanying autoimmune gastrointestinal disease(s) (n=28)	Without accompanying autoimmune gastrointestinal disease (n=246)	p-value
Age	49.1 ±10.5	45.1 ±12.3	.078
Gender, male (n,%)	1 (3.6)	20 (8.1)	NS
Vitamin B12 deficiency	11 (39.3)	39 (15.9)	.002
Iron deficiency	12 (42.9)	46 (18.7)	.003
Both deficiencies	7 (25.0)	21 (8.5)	.002
Disease duration, years	2.5 (0.5–7.0)	2.0 (0.4–5.0)	NS
Hypothyroid (on LT4 replacement)	20 (71.4)	172 (69.9)	NS

Table 5. Some characteristics of the patients with more than one additional immunological/allergic disease.

Patient	Thyroid disease	Age/ gender	Age at diagnosis	Additional autoimmune diseases
Patient1	H.T.	55/F	38	Sjögren's syndrome/CAG
Patient 2	H.T.	56/M	46	CAG/CD
Patient 3	H.T.	42/F	32	CAG/CD
Patient 4	H.T.	49/F	46	AS/rhinosinusitis
Patient 5	H.T.	41/F	37	Still disease/CAG
Patient 6	H.T.	49/F	42	CD/asthma
Patient 7	H.T.	27/F	27	Psoriasis/vitiligo
Patient 8	H.T.	56/F	49	Vitiligo/idiopathic pruritus

H.T.: Hashimoto's thyroiditis; F: Female; M: Male; CAG.Chronic Atrophic Gastritis; CD: Celiac Disease; AS: Ankylosing Spondylitis.

encountered in 10.2% of the HT patients and 3.8% of the GD patients. This was followed by allergic diseases, found in 19 (6.9%) patients with HT and 3.8% of GD patients. The most prevalent autoimmune/allergic diseases in patients with HT were chronic atrophic gastritis (7.7%), asthma (4.7%), celiac disease (2.6%), and vitiligo (1.5%). The overall prevalence of rheumatological, dermatological, and endocrinological (excluding thyroid) autoimmune diseases in patients with HT was 4.0%, 3.3%, and 1.5%, respectively (Table 3).

Although the overall levels of serum vitamin B12 were lower in patients with GD, the frequencies of both vitamin B12 and iron deficiencies were higher in patients with HT (Table 2). Hashimoto's thyroiditis patients with accompanying autoimmune gastrointestinal diseases had higher frequencies of anemia due to vitamin B12 and iron deficiency; their disease duration and current thyroid status was similar to HT patients without additional autoimmune gastrointestinal diseases (Table 4).

There was no correlation between the titers of anti-TPO or anti-Tg and the development of autoimmune and/or allergic diseases. However, the patients with dimorphic anemia had higher titers of anti-TPO compared to patients without anemia (p=0.03).

There were eight patients with more than one additional autoimmune disease, all of whom had Hashimoto's thyroiditis (Table 5).

Discussion

The patients with a primary diagnosis of an autoimmune thyroid disease are at substantially increased risk of coexisting autoimmune and allergic diseases (11, 40–42). In our Turkish unit at a tertiary care university hospital, we found that 23.7% patients with HT and 13.2% patients with GD had at least one additional clinical autoimmune and/or allergic disorder. The most prevalent coexisting organ-specific autoimmune disorders (chronic atrophic gastritis and celiac disease) involved the gastrointestinal tract, followed by allergic asthma and vitiligo. Probably, both iron and cobalamin deficiencies were also highly associated with gastrointestinal tract involvements, especially in HT patients.

Although several autoimmune diseases are individually rare, they have been estimated to collectively afflict about 3% of the population (43). The hypothesis that autoimmune diseases tend to coexist in the same person has been investigated in few studies on a large scale (11, 44). One of such studies, a cross-sectional multicenter study of 3286 Caucasian subjects (2791 with GD and 495 with HT), reported that the frequency of another autoimmune disorder in patients with GD and HT is 9.7% and 14.3%, respectively. The study reported rheumatoid arthritis as the most common coexisting autoimmune disorder. The relative risks of almost all other autoimmune diseases (systemic lupus erythematosus**,** Addison's disease, and celiac disease) accompanying GD or HT were calculated to be more than 10 times of the frequency of each autoimmune disease in the general population (11). In the present study, we found that 17.5% of HT patients had at least one additional autoimmune disease, and 6.9% had allergic diseases. The prevalence of additional autoimmune diseases and allergic diseases in case of GD patients was 9.4% and 3.8%, respectively. With respect to the overall prevalence of coexisting autoimmune diseases, our results are consistent with the aforementioned study. However, the most prevalent additional autoimmune disorder in our study was chronic atrophic gastritis, followed by celiac disease. The discrepancy between our findings and those of Boelaert et al. could be associated with several factors. First, as observed in the majority of autoimmune diseases, the development of clinical rheumatoid arthritis is collectively influenced by multiple environmental and genetic risk factors, but the exact cellular mechanisms are unclear. Geographical distribution could be one of the environmental factors possibly associated with susceptibility (45). Secondly, the diagnosis of rheumatoid arthritis is primarily based on the patient's symptomatology, and the presence of symptoms may be subjective in some cases. Since we investigated rheumatoid arthritis only in ATD patients with symptoms that could not be explained by their current thyroid function status, it is likely that we underdiagnosed latent rheumatoid arthritis in some cases. Thirdly, since we examined all patients with iron or vitamin B12 deficiency related anemia by gastroduodenoscopy, our observed prevalence of chronic atrophic gastritis and celiac disease may be higher than that reported in the literature. A study on North Italian patients with autoimmune thyroid disease also reported celiac disease (clinical, silent or latent) to be present in 5.4% of the patients (46).

The associations between autoimmune thyroid diseases and allergic disorders have been studied in a lesser detail. A Polish study unit comprising 255 patients with either HT or GD reported that 5.1% of the study population had co-existing bronchial asthma and

1.2% had allergic rhinitis (47). Our findings are consistent with these results. Another study carried out several decades ago proposed a link between chronic urticaria and autoimmune thyroid diseases, although the mechanisms of the apparent association between chronic urticaria and serological evidence of thyroid autoimmunity were not clear (48). A group of researchers has suggested that there could be a skin mast cell autoreactivity in HT patients, irrespective of autoreactive chronic urticaria (49).

Our study highlights that deficiency of cobalamin and iron, which was present in a substantial proportion (18.2% and 21.2%, respectively) of patients with HT, which could be a clinically important finding. Such a high prevalence of cobalamin and iron deficiency was not observed in the patients with GD. Moreover, the coexistence of both deficiencies was observed in 10.2% of the patients with HT. As expected, the risk of both cobalamin and iron deficiencies increases if an autoimmune disease involving the gastrointestinal tract coexists with the autoimmune thyroid disease (50). Cobalamin deficiency may exacerbate or even by itself cause symptoms such as depression, mania, irritability, paranoia, delusions, and emotional lability (51).

We could not establish a relationship between titers of anti-TPO or anti-Tg and the development of autoimmune and allergic diseases. However, a higher titer of anti-TPO (but not anti-Tg) may be associated with a higher prevalence of dimorphic anemia.

To summarize, some of the significant diseases and/or conditions coexisting with autoimmune thyroid diseases should be investigated in terms of cause-effect relationship, in future studies.

It has to be emphasized that our study has several limitations. First, the study was carried out at a single tertiary care center in Ankara. Our results may not represent the exact prevalence of autoimmune/allergic disorders coexisting with autoimmune thyroid disorders. Indeed, our aim was not to document the exact prevalence but to highlight the co-morbid conditions associated with autoimmune thyroid diseases. However, due to the recent health insurance policies in Turkey, a wide range of patients have access to healthcare in tertiary care facilities, and hence these results may provide baseline information on the prevalence of the studied associations. Secondly, our study was designed to document associated comorbidities only in symptomatic patients and did not consider latent diseases. Therefore, the subjects without symptoms but might be positive for the studied antibodies were probably not considered in our study. Thirdly, a greater study population would be required to document the more rarely encountered autoimmune diseases such as myasthenia gravis, multiple sclerosis, Addison's disease, premature ovarian failure, and so on. In addition, the comparison of coexisting diseases associated with either GD or HT may not be ideal, as the disease duration for HT was longer than GD in our study population. In addition, the increased rate of iron deficiency in HT is perhaps explained by the higher number of menstruating females in this group. The chronic atrophic gastritis could also have been caused by non-autoimmune conditions such as infection by *H. pylori*, which might be distinguished by appropriate tests. The other causes of cobalamin deficiency such as metformin use and dietary deficiency were not excluded, although these causes can be ruled out in our study population.

We do acknowledge that the value of diagnosing overt disease(s) with typical clinical signs/symptoms would seem limited but early diagnosis of the disease would facilitate its control and reduce the cost of treatment, rather than if it was diagnosed late.

In conclusion, patients with autoimmune thyroid disorders sometimes have more than just the thyroid disease, and they should be evaluated according to their symptoms since more than 20% of them could potentially have coexisting autoimmune and/or allergic diseases. The evaluation of the upper gastrointestinal tract may be useful in such patients, especially, if they have iron and/or cobalamin deficiencies.

Author Contributions

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