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A detailed analysis of thyroid disorders in autoimmune liver diseases

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ABSTRACT

Aims: Extrahepatic autoimmune diseases are frequently encountered in patients with autoimmune liver diseases (AILD). There is a very limited data in the literature on the incidence of autoimmune thyroid diseases in AILD and the characterization of thyroid diseases in these patients. This study evaluated frequency and clinical features of thyroid disorders in AILD.

Methods: We compared clinical and laboratory data and thyroid ultrasonography findings of 100 patients with AILD and 48 healthy controls.

Results: The frequency of autoimmune thyroid disease and nodularity was higher in the AILD group compared to the control group (34 % vs 12.1 %; p<0.001 and 62 % vs 41.6%; p: 0.023 respectively). The number of nodules per patient was significantly higher in the AILD group than in the control group (1.37±1.3 vs 0.88±1.3; p=0.039). Hypothyroidism was detected in 17 patients (17%) with AILD (10 newly diagnosed). Only one patient had Graves' disease.

Conclusion: In AILD, autoimmune thyroiditis are common. Thyroid pathologies are missed in most patients unless a careful and detailed examination is not performed. Thyroid ultrasonography should be performed in addition to laboratory investigations in the routine follow-up of patients with AILD.

Keywords: Autoimmune thyroid disease, autoimmune liver disease, ultrasonography, nodularity

INTRODUCTION

Autoimmune liver diseases (AILD) is a chronic inflammatory disease that causes damage to hepatocytes or cholangiocytes with immune mediated mechanisms.[1] Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) are the most common forms of AILD. Extrahepatic autoimmune diseases are frequently encountered in patients with AILD, because of shared autoimmune pathophysiological mechanisms. Underlying genetic and molecular mechanisms are not fully elucidated for concurrent autoimmune diaseases in patients with AILD. Hashimoto's thyroiditis is the one of the most common extrahepatic autoimmune diseases associated with AILD.[2] There are very limited data on occurrence of other autoimmune diseases in AILD. In these studies, the frequency of concomitant autoimmune thyroid disease in AILD patients ranged from 7% to 34% and diagnosis of autoimmune thyroid disease was based on thyroid autoantibody positivity only.[3-6] There is no study in which thyroid parenchyma and nodularity were evaluated by ultrasound in AILD. The aim of this study was to evaluate the frequency of autoimmune thyroid diseases, thyroid nodularity in patients with AILD.

METHODS

The study was carried out with the permission of Ankara University Faculty of Medicine Clinical Researches Ethics Committe (Date: 11.06.2018, Decision No: 10-670-18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Population

One hundred patients with AILD and forty eight healthy control subjects matched for sex and age were included in the study. The diagnosis of AIH was made based on the clinical, laboratory, serological and biopsy findings in accordance with international guidelines. The cholestatic enzyme elevation, anti mitochondrial antibody (AMA) positivity and biopsy findings were taken into account in the diagnosis of PBC. Cases with diagnostic doubt were not

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included in the study. The diagnosis of primary sclerosing cholangitis (PSC) was made based on clinical laboratory and magnetic resonance cholangiopancreatography (MRCP) findings.

Thyroid function tests and ultrasonographic evaluations of the patients and the control group were performed cross-sectionally. Information on concomitant autoimmune diseases and other clinical data of the patients were collected retrospectively. The diagnosis of autoimmune thyroiditis was made according to thyroid ultrasonography findings and thyroid antibodies.

Thyroid Grayscale US, Power Doppler US

All participants were evaluated using high-resolution B-mode grayscale ultrasonography, power doppler ultrasonography (Hitachi EUB 7000 HV machine with 6-13-MHz linear transducer). The nodularity and other US features (thyroid volume, internal blood flow and echogenicity) were assessed. Thyroid volume was calculated as length × width × depth × 0.479 (ml) for each lobe. Parenchymal US patterns were classified into four grades according to hypoechogenicity and heterogeneity degrees (homogeneous, mild heterogeneous, moderate heterogeneous, severe heterogeneous). Hypoechogenicity was determined by comparison of thyroid parenchyma with the echo distribution of surrounding neck muscles, and heterogeneity was defined as any region with an unclear border showing a different echogenicity from other parts of the gland. US-guided fine needle aspiration biopsy (FNA) were performed in eligible patients according to American Thyroid Association (ATA) guideline recommendations.

Laboratory Analysis

Serum thyroid stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) concentrations were measured by chemiluminescent immunometric assay (Elecsys 170; Roche Diagnostics, Indianapolis, Indiana, USA). Normal range were as follows: TSH: 0.3-4.5 µIU/ml, fT4: 10-22 pmol/l, and fT3: 3-6.5pmol/l. Serum thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) concentrations were measured using a competitive radioimmunoassay (Brahms Dynotest; Brahms Diagnostics, Berlin, Germany).

Statistical Analysis

The results were analysed using SPSS software version 20. Simple descriptive statistics were expressed as means with standard deviations. Categorical variables are expressed as actual numbers and percentages. The frequency distribution of categorical variables between subgroups was compared by the chi-square test. Numerical variables were compared by unpaired t tests. Statistical significance was defined as P<0.05.

RESULTS

The vast majority of the patients were female (91/100; 91%) and the mean age was 55.1±11.8 years in patients with AILD. Of 100 AILD patients, 67 had PBC, 25 had AIH and 8 had PSC. The frequency of autoimmune thyroiditis was higher in patients with AILD compared to controls (34/100; 34 % vs 6/48; 12.1 %; p<0.001) (Table 1). The diagnosis of 21 patients (61 %, 21/34) with autoimmune thyroiditis was made during the study period in AILD group. Hypothyroidism was detected in 17 patients (17%) in the AILD group, and 7 (7 %) of these patients were already taking levothyroxine replacement therapy for hypothyroidism. In 10 patients (2; overt hypothyroidism, 8; subclinical hypothyroidism) the diagnosis of hypothyroidism was made during the study period. Of these newly diagnosed patients, 2 patients with overt hypothyroidism and 4 patients with subclinical hypothyroidism were started on levothyroxine treatment based on clinical evaluation. There was no overt hypothyroidism in the control group and only 2 patients had subclinical hypothyroidism. Thyroid USG examination showed that moderate-markedly heterogeneous echogenicity of the thyroid gland was more common in the AILD group than in the control group (46% vs 14.5%; p <0.001) (Table 2). The frequency of thyroid nodules was significantly higher in the AILD group than in the control group (62 % vs 41.6%; p: 0.023). Furthermore the number of nodules per patient was significantly higher in the AILD group than in the control group (1.37±1.3 vs 0.88±1.3; p=0.039). Fine needle aspiration biopsy was performed in 16 of 62 patients with autoimmune liver disease and thyroid nodules. Cytological examination revealed thyroid malignancy in one patient, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) in three patients and benign lesions in others.

Table 1. Comparison of clinical parameters between AILD and control group.

Parameters	AILD (n=100)	Control (n=48)	p
Sex (male/female)	9/91	5/43	0.771
Age (yrs)	55.1±11.8	52.9±9.2	0.28
TSH (µIU/ml)	2.48±2.18	2.36±1.75	0.75
fT4 (pmol/l)	14.1±2.3	15.1±1.9	0.02
fT3 (pmol/l)	4,3±0.6	4,7±0.55	<0.0001
Concurrent extrahepatic autoimmune diasease (present/absent)	55/45	8/40	<0.0001
Autoimmune thyroiditis (present/absent)	34/66	6/42	0.006

TSH, thyroid stimulating hormone, fT4; free thyroxine, fT3; free triiodothyronine

Table 2. Comparison of ultrasonographic features between between AILD and control group

Parameters	AILD (n=100)	Control (n=48)	p
Thyroid volume (ml)	13.2±10.9	13.3±9	0.982
Thyroid parenchyma			<0.001
Diffuse homogeneous	13	16	
Mild heterogeneous	41	25	
Moderate heterogeneous	30	6	
Markedly heterogeneous	16	1	
Nodularity (present/absent)	62/38	20/28	0.023
Nodules per patient	1.37±1.3	0.88±1.3	0.039

There was no significant difference between patient and control groups in the mean thyroid volume and IgG4 levels. Subgroup analysis showed no significant difference between patients with PBC and AIH in terms of autoimmune thyroid disease (p=0,91). Additional autoimmune diseases other than autoimmune thyroid disease were detected in 30 patients in the AILD group. The most common coexisiting autoimmun disorder was Sjogren syndrome (19%) after autoimmune thyroiditis (Table 3). Other concurrent autoimmune diseases were inflammatory bowel diseases (7%), rheumatoid arthritis (4%), autoimmune skin disease (4%), scleroderma (3%), systemic lupus (3%). Only one patient had graves' disease. Six patients (6%) had concomitant malignant disease (3 patients had papillary thyroid cancer; 2 patients had breast cancer; 1 patients had over cancer). One of the patients with papillary thyroid cancer (PTC) was diagnosed during the study.

Table 3. Frequency of extrahepatic autoimmune diseases in AILD and control group

	AILD (%) (n=55/100)	Control (%) (n=8/48)
*Autoimmune thyroid disease	34 /100 (34)	6/48 (12)
Sjogren's syndrome	19/100 (19)	-
Inflammatory bowel disease	7/100 (7)	1/48 (2)
Rheumatoid arthritis	4/100 (4)	1/48 (2)
**Autoimmune skin disease	4/100 (4)	-
Systemic lupus erythematosus	3/100 (3)	-
Systemic sclerosis	3/100 (3)	-
Type 1 diabetes	1/100 (1)	-
Pernicious anemia	1/100 (1)	-

*Hashimoto thyroiditis and Graves' disease, **Psoriasis, liken planus and vitiligo

DISCUSSION

In our cohort 34% of patients with AILD were diagnosed with autoimmune thyroiditis. The majority of them are newly diagnosed patients (61%). Levothyroxine replacement therapy was started in 6 patients who were not previously diagnosed with autoimmune thyroiditis. In addition, suspicious cytologic findings were detected in three of the patients who underwent thyroid biopsy and one of them was diagnosed with papillary thyroid cancer. In our AILD cohort 55 patients had at least one autoimmune diaseae (55%).

This study mainly focuses on extrahepatic thyroidal autoimmune conditions associated with AILD using single center database. In the literature, there are many studies evaluating extrahepatic autoimmune manifestations of autoimmune liver diseases, and almost all of these studies have shown that the most common concomitant extrahepatic autoimmune disease was Hashimoto thyroiditis. Although it varies from population to population, autoimmune thyroid disease occurs in 10-12% of the population.[7] Generally, more than half of those affected have normal thyroid function tests.

The one of the largest autoimmune liver disease series was published by Muratori and colleagues.[8] In this study, at least one autoimmune disease was detected in 42.3% of 608 AILD patients (327 AIH and 281 PBS). The frequency of autoimmune thyroiditis was 19 % (24% in PBS; 15% in AIH). Wong et al.[3] reported that the prevalence of autoimmune thyroiditis was 18% in 562 patients with autoimmune hepatitis (14.1%; hashimoto thyroiditis, 3.9 %; Graves' disease) and 42% of the patients had at least one autoimmune disease. In another large cohort study by Teufel et al.[2] included 278 patients with AIH, autoimmune thyroiditis was the most common concurrent autoimmune disease (10%). Otherwise 40% of all patients had at least one autoimmune disease. Similar to our results, Floreani et al.[4] detected at least one extrahepatic autoimmune disease in 61% of patients and autoimmune thyroid disease in 23.6% of patients in their PBS cohort of 361 patients. In a recent study by Zeng et al.[9] autoimmune thyroid disease was detected in 113 of 324 (34.9%) AILD patients. In terms of frequency of concomitant autoimmune thyroid disease the most compatible results with our data were obtained in this study. In these large cohorts, the presence of extrahepatic autoimmune diseases was based on retrospective data. Among these studies, there is no study in which thyroid evaluation is as detailed as ours. In most cases, the presence of autoimmune thyroid disease was established based on patients' self-reporting. In our cohort, the higher incidence of extrahepatic autoimmune disease compared to other cohorts could be attributed to advanced thyroid examinations. The possible pathophysiological mechanisms that may explain this relationship were the presence of shared epithelial antigens and autoreactive T cells in the thyroid and liver or the cross-reactivity of thyroid autoantibodies.

In our study, we detected hypothyroidism in 17% of AILD patients. 7 of them were already on levothyroxine therapy. In line with our results, Khoury et al.[10] found that the

frequency of hypothyroidism was higher in AIH patients compared to the healthy control group (17.7% vs. 5%).

This is the first study to perform detail thyroid ultrasound examination besides thyroid function tests in autoimmune liver patients. To the best of our knowledge nodularity is more common in patients with autoimmune thyroiditis. Previous studies have shown that the risk of thyroid nodularity and thyroid cancer increases in autoimmune thyroid diseases. This is attributed to common genetic mechanisms responsible for both clinical conditions.[11] Thus high nodularity rates in the AILD group could be explained by large number of patients with autoimmune thyroid disease in our study.

One of the most striking results of our study was that 6 of the patients with AILD had a malignant disease. In patients with AILD, cirrhosis-related hepatocellular cancers are frequently encountered.[12] In a recent study by Sharma et al.[13] the most common types of cancers other than hepatic cancers in autoimmune liver patients were lymphoproliferative cancers and non-melanoma skin cancers. In accordance with the previous study, Werner et al.[14] showed that lymphoproliferative cancers were most frequently seen after hepatocellular carcinoma in patients with AIH. However, all of the cancers detected in our study were extrahepatic (3 patients had PTC, 2 patients had breast cancer and 1 had ovarian cancer). This higher incidence of extrahepatic cancer may be related to immunosuppressive therapies frequently used in autoimmune liver disease.[15] In our study, two of 3 PTC patients had autoimmune thyroid disease. The relationship between hashimoto thyroiditis and PTC has been widely debated and it is still controversial. In previos studies the association between autoimmune thyroiditis and PTC were based on retrospective pathological studies and several fine-needle aspiration cytology (FNAC) studies.[16,17] In aforementioned pathological studies it was demonstrated that the frequency of PTC increased in hashimoto thyroiditis. In addition increased TSH levels and anti-thyroid autoantibodies (ATA) titers were found to be significant and independent predictive risk for thyroid cancer. Floreani et al.[18], in their large study containing data from 921 primary biliary cholangitis patients from 2 European Centers, 94 patients (10.2 %) had hashimoto thyroiditis, 15 patients (1.6 %) had Graves' disease; 22 patients (2.4%) had multinodular goiter; 7 (0.8%) patients had thyroid cancer. Nowadays, with the widespread use of thyroid ultrasonography, thyroid nodules has been detected more frequently and the prevalence was up to 68% using high-frequency US examination.[19,20] We thought that the higher incidence of nodularity and thyroid cancer in our patients compared to the previous studies may be related to our detailed thyroid USG examinations.

The most important contribution of this study was the initiation of levothyroxine replacement in 6 patients with hypothyroidism who were unaware of the diagnosis. In addition papillary thyroid cancer was detected in one patient and she underwent total thyroidectomy. This demonstrates the usefulness of thyroid ultrasound assessments in patients with AILD as well as routine biochemical tests.

In our study, IgG4 levels were not different in AILD and control groups. The low IgG4 titers in the AILD group were associated with the fact that the majority of AILD patients were under immunosuppressive therapy.

The limitations of our study include the retrospective nature of data collection and lack of other autoantibody levels and detailed clinical features in AILD patients.

CONCLUSION

This is the first study in which detailed thyroid examinations were performed in patients with AILD. We demonstrated that AILD has a strong association with extrahepatic autoimmune diseases especially with autoimmune thyroid disease. Moreover this study showed that thyroid nodularity, thyroid cancer and extrahepatic other cancers are more frequent in patients with AILD. In the light of these findings, it is recommended that in all patients with AILD, besides biochemical procedures, thyroid ultrasonography should be added to the routine examinations.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara University Faculty of Medicine Clinical Researches Ethics Committe (Date: 11.06.2018, Decision No: 10-670-18).

Informed consent: Written informed consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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