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Prevalence of coexisting autoimmune disease in patients with autoimmune thyroid disease

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Abstract

Introduction: Autoimmune thyroid disease (AITD) including Hashimoto's thyroiditis (HT) and Grave's disease (GD) is a common immune-mediated disease. It has an association with the increased incidence of other autoimmune diseases.
Objectives: The purpose of the current study was to describe the prevalence and distribution of non-thyroidal immune-mediated disease in patients with AITD.
Patients and Methods: This study was a retrospective. All patients who were diagnosed with AITD in their thyroid biopsy were enrolled. The information about the coexisting disease was obtained by a trained physician using a questionnaire. The confirmed data about the disease in six systems were documented in the questionnaire
Results: Of 293 AITD patients, 250 eligible cases with an average age of 48.7 years old including 23 male patients and 227 female patients were included in the study. We found 224 patients did not have a coexisting autoimmune disease. The 26 remaining patients were; 17 patients with skin disease, 3 patients with rheumatologic disease, 3 patients with endocrine disease and 2 patients with hematologic disease and none of the patients had neurologic disease. The prevalence of the disease increased with age and had no relation to gender.
Conclusion: Our study showed the prevalence of non-thyroidal immune-mediated disease increased in AITD patients. Autoimmune skin disorders are the most common disease in these patients, followed by rheumatologic and endocrine diseases.

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Introduction

Thyroiditis is a disease usually occurs between 30–50 years old. It affects females more than males (1). It could be presented with various features such as enlargement or tenderness of thyroid gland, fever, hyperthyroidism or hypothyroidism. Different etiologies can cause thyroiditis. Autoimmune thyroid disease (AITD), viral and bacterial thyroid disease, drug-induced thyroiditis are the common causes (2,3).

AITD including Hashimoto's thyroiditis (HT) and Grave's disease (GD) is the most common autoimmune disease. It is estimated that 5% of all people and 10%-20% of women are suffering from AITD during their lifetime. Environmental conditions and genetic susceptibility are involved in the development of them (4, 5). Both HT and GD have a great association with HLA-DR3. HT is a chronic autoimmune disease that decreases the function of the thyroid gland causing hypothyroidism. It is associated with lymphocytic infiltration and increased production of thyroglobulin antibody (TG-Ab) and thyroid peroxidase antibody (TPO-Ab) (6). GD is the most common cause of hyperthyroidism. B-cells infiltrates the thyroid glands and producing anti-TSH receptor autoantibody (thyrotropin receptor autoantibody) stimulates it (7). Thyroid disease is diagnosed with thyroid function blood tests and imaging modalities such as ultrasonography and thyroid scan tests. If

Key point

In the current study, the coexistence of non-thyroidal autoimmune disease in 283 autoimmune thyroid disease (AITD) cases was investigated. The results showed that autoimmune dermatology, rheumatology, and endocrine diseases are frequently seen in AITD patients.

these tests were not helpful or the result was suspicious further investigations such as biopsy will be performed (8).

Various studies confirm an association between AITD with an increased incidence of another autoimmune disease in patients and even their relatives (9). This coexistence has been seen in different systems. In the gastrointestinal tract, celiac and primary biliary cirrhosis are prevalent in AITD patients (10, 11). In 17.5% of AITD patients, the rheumatoid antibody is detected. Also, rheumatologic diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome, fibromyalgia, and rheumatoid arthritis are more frequent (12-14). Skin disorders such as vitiligo and alopecia areata (AA) may be seen especially in patients with younger ages and severe diseases, have a great association with AITD (15-17). This condition is the same for another disease like pernicious anemia, sarcoidosis and type 1 diabetes mellitus (18). Unlike many autoimmune diseases, there was no correlation between multiple sclerosis and AITD (19). However, a study conducted in France in 2017 investigated GD and HD patients and they found that these diseases are linked with a higher occurrence of myasthenia gravis disease (MG). Therefore there might be a relation among AITD with neurologic autoimmune disease too (20). In addition, several studies investigated the prevalence of other autoimmune diseases in these patients and their first-degree relatives. The prevalence of extra-hepatic autoimmune disease of the thyroid gland, Sjögren's disease, Reynaud's disease, and psoriasis was higher in autoimmune hepatitis patients (21). The outcome was the same in multiple sclerosis and pemphigus patients (22,23). Numerous studies are confirming the higher rate of autoimmune diseases such as AITD in patients with celiac disease (24). In a study conducted in the United Kingdom, Somers et al looked into the co-occurrence of autoimmune disease. The results demonstrate an increased incidence of thyroiditis, rheumatoid arthritis and type 1 diabetes mellitus in the subjects comparing to community-based expectations (25).

Objectives

Epidemiologic studies claim worldwide increasing rate of autoimmune disease including autoimmune thyroiditis (26). Besides, the early diagnosis of these diseases will improve the prognosis. Therefore, knowledge about the prevalence and distribution of the disease will be helpful in screenings and recognition of these patients. The uncertainty and lack of enough evidence about the actual information led us to perform this epidemiologic study.

Patients and Methods

Study design

This study was retrospective and performed in Alzahra hospital from 2012 to 2019. Around 250 patients with autoimmune thyroid including 23 males aged between 32 and 62 years and 227 females aged between 22 and 68 years were included in the study. Subjects were patients who were suffering from thyroid disease and conducted a biopsy for confirmation.

Patients who did not want to contribute to the study, the ones with an uncertain pathology result, patients who passed away during the study and patients suffering from chromosome syndromes (Down's syndrome, Klinefelter syndrome, Turner's syndrome or Trisomy 21 syndrome) were excluded from the study.

After the initial laboratory tests and other diagnostic evaluations, to confirm the diagnosis of ATD, the patients were referred to the pathology department. Based on the patient's condition biopsy was obtained whether via fine-needle aspiration or surgery. These samples were stained and prepared properly. Then an experienced pathologist reviewed and interpreted them. Among all cases, patients with a certain result of AITD were collected. To obtain the disease data including demographic characteristics, co-morbidities and coexisting disease a questionnaire was prepared. The questionnaire included two sections. First, the demographic data which was completed using hospital registration information. The second part of the questionnaire concerned about coexisting autoimmune disease. A trained physician completes this part using patients' confirmed data. The co-morbidities were classified into six major groups; dermatologic autoimmune disease, hematologic autoimmune disease, endocrine autoimmune disease, rheumatologic autoimmune disease, gastrointestinal autoimmune disease, and neurologic autoimmune disease. All these data were collected and tracked on a worksheet.

Ethical issues

The study was in accordance with the Declaration of Helsinki and its later amendments. This paper was extracted from the M.D., thesis of Mona Namazi at the Isfahan University of Medical Sciences. All the participants were informed about the study aims and written informed consent was obtained from them. This study was approved by the ethics committee affiliated with the Isfahan University of Medical Sciences (#IR.MUI.RESEARCH.REC.1397.174).

Statistical analysis

Data recorded on these worksheets were transferred to SPSS (Statistical Package for the Social Sciences v25.0, SPSS Inc. Chicago, IL). Analysis was performed in two sections: descriptive analysis such as age, gender and frequency and percentage of the co-morbidities. Also, the correlation between the incidences of the co-existence of the diseases was checked using the Pearson's correlation coefficient and chi-square tests. In all statistical analyses, *P* value was considered less than 0.05.

Results

This cross-sectional study was conducted on those patients referred to the pathology ward of Al-Zahra hospital who

underwent thyroid surgery or fine-needle aspiration due to any autoimmune thyroid disorder. Qualitative data were analyzed by descriptive statistics (frequency and frequency percentage) and Pearson's correlation coefficient and chi-square tests.

Among all the samples, 10 (3.4%) patients were excluded due to death and 33 (11.2 %) cases were excluded because they did not want to participate. Therefore of 293 patients, 250 (85.3%) patients selected for this study with average age of 48.7±9.4 years.

Of 250 patients, 227 (90.8%) were female and 23 patients (9.2%) were male. The descriptive statistical analysis of qualitative data indicated that 26 patients (10.4%) suffered from autoimmune diseases. No one reported the simultaneous co-existence of more than two autoimmune diseases. Table 1 shows the relative frequency of autoimmune diseases in the studied patients. As demonstrated, the autoimmune dermatologic disease had the highest co-existence with thyroid patients (17 patients, 6.8%) following by rheumatologic and endocrine disease (3 patients, 1.2%), gastrointestinal disease (3 patients, 0.8%). The lowest prevalence was the hematologic disease with co-existence in only one patient (0.4%) and there was not any patient with neurologic disease.

As reported in Table 2 the results of the Pearson's correlation coefficient, a significant positive correlation between the relative frequency of autoimmune diseases and the patient's age ($r = 0.45$, $P = 0.047$) was detected. In other words, the risk of autoimmune diseases increases with increasing age. This correlation is the same for both genders ($P < 0.05$).

Although the incidence rate is much higher in women, the results of the chi-square test showed no significant relationship between the frequency of co-existing autoimmune diseases and gender ($P = 0.70$).

Table 1. Relative frequency of autoimmune diseases in the studied patients

	Frequency percentage	Frequency
Without autoimmune diseases	89.6	224
Autoimmune skin diseases	6.8	17
Autoimmune Digestive system disease	0.8	2
Autoimmune Rheumatologic disease	1.2	3
Autoimmune hematologic diseases	0.4	1
Autoimmune neurologic disease	0	0
Autoimmune Endocrine disease	1.2	3
Total	100.0	250

Table 2. The relationship of the relative frequency of autoimmune diseases with age ($P < 0.05$)

		Autoimmune disease
Age	Pearson's correlation coefficient	0.047
	Sig. (2-tailed)	0.456
	N	250

Discussion

The object of the current study was to describe the prevalence of the co-existence of autoimmune diseases in AITD patients. Additionally, we aimed to investigate the correlation of this condition with age and gender. The study was conducted on 250 patients and as mentioned in the results, 10.4% of the AITD patients were suffering from another autoimmune disease at the same time. These diseases were related to different systems. Autoimmune skin disease, rheumatologic disease, endocrine disease, digestive tract disease, and hematologic diseases had the highest to the lowest relative frequency respectively. Besides, there was no one with neurologic autoimmune disease. This co-existence increases with age patients getting older and had no relation to gender.

There have not been many studies conducted in Iran concerning the exact prevalence of autoimmune diseases, while the studies which have been done worldwide report different rates. However, the incidence of autoimmune diseases is increasing, the prevalence is less than 10% (27, 28). In our study 10.4% of AITD patients had a co-existing disease. The chance of having a second autoimmune disease is higher than having a single disease. This would confirm the correlation between these diseases.

Common autoimmune dermatologic diseases associated with AITD are AA, vitiligo and chronic idiopathic urticaria. Many studies have been done regarding the association between AA and AITD. In a survey in Taiwan, the incidence of AITD was significantly higher than the normal population (29). These results were confirmed by Han et al in a Korean study that explored AITD in AA patients with the increased incidence of both Graves' disease and HT in the study group (15). Vitiligo is another skin disease with a significant relationship with AITD especially HD. Recent studies on these patients reveal that up to 34% of them may be suffering from HD too(16). In 2017 Vachirman et al studied 325 vitiligo patients. In about 19.7% of them the anti-TPO antibody was positive and in 19.4% of them anti-TG antibody was positive (30). Chronic idiopathic urticaria (CIU) is another skin disorder with an immunological basis. Various studies reported an association of this disorder with AITD. A review in 2013 reported a 1.2% - 4% prevalence of GD in CIU patients (31). All these studies claim a high prevalence of autoimmune skin disorders in AITD patients. This concordance in our study was seen in 6.8% of these patients.

Surveys demonstrate that the risk of rheumatic diseases in AITD patients is above the normal population. Rheumatoid arthritis, SLE, Sjögren's syndrome are linked with AITD. For example in rheumatoid arthritis patients, it is 1.3 times higher (25). Study on AITD patients, rheumatoid antibodies have been checked and the results demonstrated high values of anti-nucleotide antibody and anti-Ro/SS-A (32, 33). Antonelli et al in Italy investigated SLE patients for thyroid diseases. They showed the odds ratio of subclinical hypothyroidism and positive anti-TPO

antibody compared to the general population were 4.5 and 2.6, respectively. Also, 6.4% of female SLE patients were suffering from HT or GD (33). A recent review in 2018 about Sjögren syndrome claimed that the prevalence of AITD in SS patients could be even up to 10% - 30% (34).

Autoimmune disease coexistence with AITD may be a manifestation of autoimmune polyendocrinopathy syndrome (35). Also, type 1 diabetes mellitus (T1DM) have been proven to have a great association with AITD. Kekleas et al in a review mentioned that AITD in T1DM patients could be 2-4 times higher than the normal population (36). Endocrine autoimmunity in our study as a co-morbidity seen in 1.2% of AITD patients. A study in the Iranian population that explored T1DM (as the most common endocrine autoimmune disease) reported an overall prevalence of 0.04% in the normal population (37). These statistics confirm the high prevalence of endocrine diseases in AITD however the rate of coexistence of our study is higher in comparison with prior studies.

Prior studies showed coeliac disease, as an autoimmune gastrointestinal disease is related to AITD. In a study conducted in the Netherlands, 4.1% of celiac patients have also suffered from AITD (38). Roy et al did a review study about immune-mediated thyroid disease in coeliac patients. Around 2.7% of CD adult patients were also suffering from AITD. These data are in favor of a higher prevalence of the AITD in CD patients (39). In our study, 0.8% of subjects were CD patients. This is almost similar to the rate of the normal population (0.5%-1%) (40).

Conclusion

While the coexistence between AITD and neurologic and hematologic autoimmune diseases has been noticed, in our study no patient with neurologic diseases was detected and there was only one patient with hematologic autoimmune disease.

Limitations of the study

Our investigation was conducted in a limited number of patients, therefore a greater number of participants especially more male patients would have led to more generalized results.

Authors' contribution

PR: study design, AA: patient diagnosis and selection, PR, AB, PH, SE, MH, AN, MD: Pathology and IHC review, MN: data collection and analysis, AZ, SF: Writing and editing, AB: Supervision and revision.

Conflicts of interest

The authors declare that there were no conflicts of interest. The authors are responsible for the writing and content of this article.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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