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Original Research Article

Assessment of the Clinical Relevance of Antithyroid Antibodies in a Sample of 130 Moroccan Patients

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Abstract: Autoimmune thyroiditis (AIT) is the most common organ-specific autoimmune diseases in humans. It is characterized by the presence of circulating antithyroid autoantibodies (TAAs). The aim of our study was to evaluate the diagnostic performance of antithyroperoxidase (anti TPO), antithyroglobulin (anti TG) and anti TSH receptor (anti RTSH), during thyroid and non-thyroid autoimmune diseases (AID). This is a descriptive retrospective study over a period of 30 months (January 2019 June 2021), which included 130 adult patients hospitalized at the Ibn Sina University Hospital in Rabat. The average age was 46 ± 15 years. Women accounted for 107 cases (82.30%), representing a sex M/F ratio of 0.21. Our series showed 82 patients who were in euthyroidism, 29 in hypothyroidism and 19 in hyperthyroidism. Anti-TPO positive were found in 118 patients, of whom 90.7% (n=107) had Hashimoto's thyroiditis and 6.7% (n=8) had Basedow's disease. Of the 66 patients with anti-TG-positive drugs, 89.4% (n=59) had Hashimoto's thyroiditis and 7.6% (n=5) had Basedow's disease. Anti-RTSH antibodies were found in 6 patients, all with Basedow's disease. AITs were associated with autoimmune non-thyroid conditions in 59.23% (n=77) of patients; type 1 diabetes was most prevalent in 30.76% (n=40). In conclusion, a high presence of TAAs was found in the context of euthyroidism with a wide range of AIDs. This requires careful interpretation in order to accurately determine their actual clinical significance outside an AIT context.

Keywords: Antithyroid antibodies, euthyroidism, hypothyroidism, autoimmune disease, autoimmune thyroiditis.

INTRODUCTION

Autoimmune thyroiditis is common. It accounts for 30% of organ-specific autoimmune diseases and a wide spectrum of clinico-biological manifestations, sometimes completely opposed, such as hypothyroidism and hyperthyroidism [1]. The only element common to all these forms of diseases is the presence of intra-thyroid lymphocyte infiltrate. This infiltrate is most often associated with high levels of circulating antibodies specific for thyroid autoantigens [2].

Autoimmune disease (AID) usually occurs on a predisposed genetic basis and may be induced by epigenetic factors [3]. Abnormalities in thyroid function and anti-thyroid autoantibodies (TAAs) have been frequently reported in patients with systemic autoimmune rheumatic diseases, such as Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus and systemic scleroderma [4, 5, 6]. The objective of this work is to evaluate the diagnostic performance of TAA antithyroperoxidase (Anti TPO), anti-thyroglobulin (Anti TG) and anti-TSH receptor (Anti RTSH), during thyroid and non-thyroid autoimmune pathologies, in order to propose a course of action that would optimize the management of patients.

MATERIALS AND METHODS

This is a retrospective cross-sectional observational study with a descriptive aim over a period of 30 months (January 2019- June 2021), which focused on a sample of 130 adult patients hospitalized at the Rabat CHUIS with TAAs.

Inclusion and exclusion criteria

The following were included in the study:

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- Adult patients whose antithyroid autoimmunity assessment was carried out at the central biochemistry laboratory (CBL) of Ibn Sina University Hospital of Rabat and who had TAAs.
- The following were excluded from the study:
- Patients without TAA.
- Patients with incomplete clinical or laboratory records.

Patient-specific data were collected using an operational data sheet containing socio-demographic, clinical, biological and medical imaging data.

Criteria for the assessment

Biological parameters

The following were analyzed: ultra-sensitive thyroid stimulating hormone (TSHus), free thyroid hormones T4 and T3 (T4L and T3L) and TAAs (anti-TPO, anti-TG, and anti-RTSH). The analytical method used for hormone dosing (TSHus, T4L and T3L), detection and quantification of TAA, anti-TPO and anti-TG, was microparticulate chemiluminescence (CMIA) on the Architect i2000, Abbott® self-analyser. Anti-RTSH antibodies were made by chemiluminescence (human TRAK LIA® Brahms). The positive TAA thresholds are anti-TPO > 5.61 IU/mL, anti-TG > 4.11 IU/mL and anti-RTSH> 1 IU/l [7]. The reference ranges for hormone dosing are [7]: TSH us [0.35-4.94 IU/L], T4L [7.0-14.8 ng/L] and T3L [1.71-3.71 ng/L].

Case definitions used

Dysthyroidism

This is the set of thyroid diseases characterized by a disorder that may affect thyroid hormone secretion. This disorder results in an increase or decrease in the plasma level of free thyroid hormones responsible for multiple and varied clinical manifestations that are grouped under the term hyperthyroidism or hypothyroidism [8].

a. Hypothyroidism is a deficiency of thyroid hormones. It can be congenital or acquired. Hypothyroidism is said to be subclinical, or frustrated, when TSH levels are elevated, with a normal concentration of T4L. Proven hypothyroidism is defined as an elevation of TSH above the high normal value, often associated with a decrease in T4L and T3L [9].

b. Hyperthyroidism is defined by a decrease in TSH below the low normal value, often associated with an exaggerated production of thyroid hormones (T4L and/or T3L). All clinical signs secondary to hyperthyroidism are grouped under the name thyrotoxicosis [10].

Thyroid autoimmunity

Diagnosis of thyroid autoimmunity was retained for:

- ✓ Disturbances of TSHus, free thyroid hormones (T4L and T3L), associated with the presence of TAA (Anti TPO, Anti TG and Anti RTSH). And
- ✓ Clinical signs of thyroid disorders (hypothyroidism or hyperthyroidism/thyrotoxicosis) and/or the presence of goiter or thyroid nodule.

Basedow's disease was defined on the basis of the following criteria [11]:

- ✓ Clinical signs of hyperthyroidism (signs of general hypermetabolicity)
- ✓ Low TSH < 0.35 IU/L
- ✓ High T4L and T3L concentrations > 14.8 ng/L and > 3.71 ng/L respectively
- ✓ The presence of anti-RTSH.

Hashimoto's thyroiditis [11]:

- ✓ The presence or absence of signs of hypothyroidism
- ✓ The presence of anti-TPO and/or anti-TG.
- ✓ High TSH > 4.94 IU/ L or within normal limits.
- ✓ T4L and T3L low or within normal limits.

Statistical analysis

The data entry and statistical analysis were carried out on Jamovi software version 2.2. Qualitative variables were described in terms of numbers and percentages. The distribution of the quantitative variables was judged on the basis of a shapiro-wilks test. The significance threshold was set at $p< 0.05$. Quantitative Gaussian variables were described by mean and standard deviation (age). Other quantitative variables in non-Gaussian distributions were described by median and interquartile intervals.

Ethics

The different stages of our study were carried out in strict compliance with the anonymity and confidentiality of patients' personal data.

RESULTS

The average age of the series was 46 ± 15 years with extremes of 17 to 89 years. The most represented age group was between 20 and 60 years (80%), of which 31.5% were in the 20-40 age group, and 48.5% in the 40-60 age group (Figure 1).

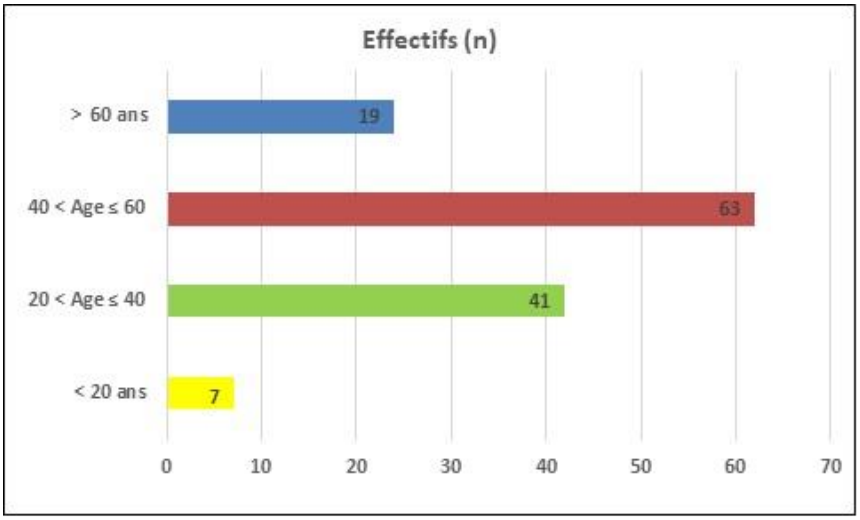

Figure 1: Distribution by age group.

For sex we found a clear female predominance with 107 cases (82.30%), i.e. a sex ratio H/F of 0.21. Our series showed 82 cases of patients who were in euthyroidism (absence of clinical signs, normal TSHus, normal T4L and T3L), 29 cases of hypothyroidism, and 19 cases of hyperthyroidism. Among patients with TPO antibodies, 62.7% (n=74) had euthyroidism, 23.7% (n=28) had hypothyroidism, and 13.6% (n=16) had hyperthyroidism. Patients with anti-TG antibodies, 62.2% (n=41) were euthyroid, 24.2% (n=16) were hypothyroid and 13.6% (n=09) were hyperthyroid. The presence of anti-RTSH antibodies (n=6) was associated with hyperthyroidism in 100% (n=6) of cases (Table 1).

Table 1: Anti-thyroid antibodies and thyroid profile

	Thyroid profile			
Type of TAA	Euthyroidism n (%)	Hypothyroidism n (%)	Hyperthyroidism n (%)	Total n (%)
Ac anti-TPO n= 118	74 (62.7%)	28 (23.7%)	16 (13.6%)	118 (100%)
Ac anti-TG n= 66	41 (62.2%)	16 (24.2%)	09 (13.6%)	66 (100%)
Ac anti-RTSH n = 06	0 (0%)	0 (0%)	06 (100%)	06 (100%)

Autoimmune thyroid pathologies associated with TAA in our patients were mainly represented by Hashimoto's thyroiditis found in 109 patients (83%), and Basedow's disease found in 10 patients (8%). Of the 118 patients with anti-TPO positive, 90.7% (n=107) had Hashimoto's thyroiditis, and 6.7% (n=8) had Basedow's disease. Of the 66 patients with positive anti-TG, 89.4% (n=59) had Hashimoto's thyroiditis, and 7.6% (n=5) had Basedow's disease. Anti-RTSH antibodies were found in 6 patients, all of whom had Basedow disease (Table 2).

Table 2: Profile of anti-thyroid autoantibodies and of autoimmune thyroiditis

Type of TAA	**Hashimoto's thyroiditis (n=109)**	**Basedow disease (n=10)**
Ac Anti-TPO n=118	107 (98.16%)	8 (80%)
Ac Anti-TG n=66	59 (89.4%)	5 (50%)
Ac anti-RTSH n=6	0 (0%)	6 (60%)

Among patients with positive TAA, 59.23% (n=77) of these had autoimmune non-thyroid conditions; type 1 diabetes was most commonly associated with 30.76% (n=40), rheumatoid arthritis 5.38% (n=7), systemic lupus erythematosus 4.61% (n=6), primary biliary cholangitis, autoimmune hepatitis, celiac disease, Biermer disease, pemphigus and scleroderma were associated to a lesser degree (Table 3).

Table 3: Autoimmune non-thyroid pathologies associated with TAA

Thyroid profile	Autoimmune non-thyroid pathologies associated with TAAs									
	T1D (n=40)	RA (n=7)	SLE (n=6)	PBC (n=6)	HAI (n=3)	CD (n=4)	BD (n=3)	Pemphigus (n=3)	Scl (n=3)	Total
Hypothyroidism	4	3	1	0	1	2	3	1	2	17
Hyperthyroidism	8	1	0	1	0	0	0	0	0	10
Euthyroidism	28	3	5	5	2	2	0	2	1	50
Total	40	7	6	6	3	4	3	3	3	77

Abbreviations: T1D: type 1 diabetes, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, PBC: primary biliary cholangitis, CD: celiac disease, BD: Biermer's disease, Scleroderma.

DISCUSSION

Autoimmune thyroiditis (AIT) is common in clinical practice. It is characterized by two main aspects of clinico-biological expression: hypothyroidism and hyperthyroidism [1, 12]. The two most common etiologies of AIT are Hashimoto's thyroiditis (HT) and Basedow's disease (BD) [13]. The presence of intra-thyroid lymphocyte infiltration, and circulating antithyroid autoantibodies are the common elements in these forms of disease [2]. AIT usually occurs on a predisposed genetic basis and may be induced by environmental factors [3]. The average age of our series was 46 ± 15 years with extremes of 17 to 89 years, this average is lower than that observed in the study of Fallahi P. and all, conducted in Italy which was 54 ± 16 [14].

The prevalence of TAA increases with advancing age in women [4,15]; a peak is observed around age 60 [16]. The most represented age group in our series was between 20 and 60 years (80%), of which 31.5% for the age group 20 40 years, and 48.5% for the age group 40 60 years. In the study by Martin and all, the results showed that 7.9% of patients with TAA were under 20 years old, 32.9% between 20 and 40 years old, 30.9% between 40 and 60 years old, and 28.3% of patients were over 60 years old [17]. These results showed that age is a risk factor for the development of thyroid autoimmunity, the most exposed age group is between 20 and 60 years.

Our series revealed a clear female predominance, i.e. an M/F sex ratio of 0.21, similar to those found in the study of Sattar et al, and in the study of Chabchoub and all which were respectively 0.25 [15], and 0.20 [18]. The study by Fallahi P. and all, found a higher sex ratio estimated at 0.33 [14]. Concerning the TAAs, the results reported in our series show that the anti-TPO antibodies and the anti-TG antibodies are associated with HT of the order of 98.16% and 89.4% respectively. These positivity rates of anti-TPO antibodies and anti-TG antibodies were similar to those found in the Toubert *et al.*, study (95% anti-TPO) [19], the Nakamura *et al.*, study (81.6% anti-TPO and 96.9% anti-TG) [20] and those of Sattar *et al.*, (86% anti-TPO) [15].

However, the appearance of anti-TPO antibodies is the first abnormality observed in HT, even before the appearance of signs of dysthyroidism. Their presence in more than 90% of cases confers on these antibodies a diagnostic marker for HT. Therefore, given the percentages cited, it would be ideal to prescribe them alone in the face of a suspicion of HT, without being associated with the anti-TG antibodies which would find their place in the diagnosis, in the absence of anti-TPO [21]. As for BD, it accounted for 8% of dysthyroidism in our series. Anti-RTSH antibodies were prescribed in 7 patients, of which 6 were positive or 60%. Anti-TPO antibodies and anti-TG antibodies were present in 80% and 50% of patients with BD, respectively. These results, despite the low number of people found, appear to be close to those described in the literature, by Toubert and all. (80% anti-RTSH, 70% anti-TPO, and 30% anti-TG) [19], and Nakamura and all. (89% anti-RTSH, 81% anti-TPO, and 80% anti-TG) [20].

Anti-TPO antibodies are detected in 70% to 85% of BD cases, moreover anti-TG antibodies are detected at a rate not exceeding 50%, therefore the diagnosis of a typical form of BD is based on the detection of anti-TPO, TSHus and signs of thyrotoxicosis [21]. Anti-RTSH antibody testing is unnecessary for the diagnosis of a typical form of BD. However, it may be of interest in some atypical clinical forms, such as isolated baseowian ophthalmopathy with euthyroidism, and for monitoring and evaluating prognosis [21]. The association between AIT and AID specific or non-specific organ is widely reported in the literature [4, 22]. The most frequently described associations according to studies are type 1 diabetes (T1D), Sjögren's syndrome, celiac disease, primary biliary cholangitis and Biermer's disease [11, 15, 23].

In addition, concerning the association of AIT and AID, our series showed that 77 patients with TAA had an associated non-thyroid AID, or 59% of cases. It is noted that among them, 50 patients or 65% were in euthyroidism. T1D remains the most common AID associated with AIT, and its frequency varies between studies [18, 24, 25]. In our series, the frequency of T1D was 31%, which is similar to that reported by Chabchoub and all. at 39.7% [18], and Kabbaj and all. at 31.5% [24]. The frequency of this association was much lower in the Fallahi and all. study of about 1% [16], and that of Sattar and all. of about 4.3% [14].

The other AIDs associated with AITs in our series are rheumatoid arthritis 5.38% (n=7), systemic lupus erythematosus 4.61% (n=6), primary biliary cholangitis 4.61% (n=6), autoimmune hepatitis 2.3% (n=3), celiac disease 3.1% (n=4), Biermer disease 2.3% (n=3), pemphigus 2.3% (n=3) and scleroderma 2.3% (n=3). The series reported in the literature for the association of AIT with RA, SLE, PBC, HAI, BD, pemphigus, and Scl showed highly variable percentages [14, 16, 23-28]. The high prevalence of TAAs in patients with autoimmune diseases in addition to AITs is probably due to the common pathophysiological mechanism in the development of autoimmunity, in the literature some authors estimate the prevalence of TAAs in patients with systemic AID at about 30% [29], but would certainly be variable depending on the nature of the associated disease and also the population.

Patients with TAA in euthyroidism should be regularly monitored to assess their thyroid function through the assay of TSHus, as well as screening of others AID be indicated if subjects with AIT have new or non-specific symptoms. It is also important to mention the impact of genetics and epigenetics in the occurrence of AIT, particularly the groups of the major histocompatibility complex II. Indeed, the HLA B8 DR3 haplotype is associated with BD, the HLA B8 DR5 haplotype with HT, thus increasing the relative risk of each of these pathologies [30].

Other factors such as antecedent AID, stress, exposure to ionizing radiation, history of infections, and iatrogenic factors are also linked to the onset of AIT [22, 31 34, 29]. Exposure to endocrine disruptors may also be involved in the onset of AIT, by affecting thyroid gland function through multiple mechanisms: by interfering with the function of hormone synthesis, transport or excretion; by mimicking the action of these hormones, or by inhibiting binding to their receptors [35].

CONCLUSION

Through our study, a pleiotropy of association of TAAs with a wide range of AIDs was found. TAAs are prescribed in the context of AIT screening, and their presence in the context of euthyroidism was found to be largely responded to as shown in our study (presence of anti-TPO and/or anti-TG without dysthyroidism). This requires careful interpretation in order to accurately determine their actual clinical significance outside an AIT context.

Conflict of Interest

None.

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