The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

EASi™
European Autoimmunity
Standardisation Initiative


ThermoFisher
SCIENTIFIC

The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

Pabst Science Publishers
Lengerich, Berlin, Bremen, Miami,
Riga, Viernheim, Wien, Zagreb

Bibliographic information published by Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

http://www.pabst-publishers.de

Printing: MercedesDruck, Berlin
Typesetting: Hilmar Schlegel, Berlin
Cover: Agentur für zeitgemäße Kommunikation Kaner Thompson
www.kanerthompson.de

ISBN 978-3-89967-770-6

Autoimmune thyroid diseases

Joana Rema, João Pedro Ramos, Carlos Dias

1 Introduction

Autoimmune thyroid diseases (AITD) include a number of conditions that have in common cellular and humoral immune responses which are aberrantly directed against the thyroid gland. Classically, AITD includes Hashimoto's and, Graves' diseases, both of which involve a significant infiltration of the thyroid by T or B cells with the production of thyroid-reactive autoantibodies, and the resulting clinical manifestations of dysfunctional hypo or hyper thyroid function. Other clinical variants of AITD include atrophic thyroiditis, postpartum thyroiditis, drug-induced thyroiditis (such as interferon-induced and amiodaron-induced), polyglandular autoimmune syndromes, and the so-called subclinical thyroiditis, defined by the presence of thyroid antibodies (TAbs) with no obvious clinical disease.

Autoimmune thyroid diseases (AITDs) are the most prevalent autoimmune diseases, affecting up to 5 % of the general population in western countries. Hashimoto's thyroiditis (HT) and Graves' disease (GD) are amongst the most common endocrine disorders in childhood and adolescence. They tend to be familial and are up to six times more frequent in women than in men.

2 Etiology and pathogenesis

The etiology of AITD includes the interaction between genetic and environmental susceptibility or triggering factors. It has been postulated that about 80 % of the susceptibility to develop AITD is attributable to genetic factors, while environmental factors would contribute to about 20 %. Whereas iodine intake, stress, infection and food or ambient toxins constitute environmental factors, genetic factors play an important role in the development of AITD as shown by twin and family studies. Although there is a strong genetic basis, the pattern of inheritance seems complex. Human HLA antigens have been associated with these diseases. Genome-wide screening and linkage analyses have identified several chromosomal regions that are linked to AITD.

3 Clinical manifestations and diagnostic criteria

The AITD may present with a wide spectrum of clinical symptoms and can be associated with a euthyroid, hypothyroid or thyrotoxic status. The most clinically significant forms of AITD are Hashimoto's and Graves' diseases, and their most relevant clinical signs and symptoms are summarized in Table 1. Hashimoto's disease is usually an insidious syndrome where the clinical presentation is marked by hypofunction, whereas Graves' disease is of a more sudden onset where palpitations and nervousness are common first symptoms, but in both conditions thyroid dysfunction can appear more or less noticeably and with a more or less perceivable goitre, usually painless and without pressure symptoms.

Systemic manifestations are mostly related to thyroid dysfunction and a detailed medical history should provide the necessary clinical clues. The basic evaluation is the same as recommended for the diagnosis of hypo or hyperthyroid function and patients should be asked for those symptoms as mentioned in Table 1, as well as about their previous prescription drug treatment. Whenever the diagnosis of thyroid dysfunction has been previously defined, it is fundamental to confirm it by history and by documenting pre-treatment analytical abnormalities. It should always be remembered that patients who have been under treatment for a long time have often forgotten their clinical past, the reasons for the therapy and their response to it.

Basic analytic evaluation should start with thyroid-stimulating hormone (TSH) and free thyroxine (fT4) measurements. TSH assay should be sensitive enough to accurately differentiate euthyroid from a hypo or hyperfunctional status. Mild hypothyroidism can be detected by a normal fT4 and a slightly elevated serum TSH.

Table 1. Main signs and symptoms of Graves' and Hashimoto's Diseases.

Graves' Disease (symptoms of hyperthyroidism)	**Hashimoto's thyroiditis** (symptoms of hypothyroidism)
Anxiety	Decreased concentration ability
Irritability	Depression
Sleeping difficulty	Excessive sleepiness
Fatigue	Leg swelling
Rapid or irregular heartbeat	Bradychardia
Heat sensitivity	Cold intolerance
Weight loss, despite normal food intake	Modest weight gain
Goitre	Goitre
Brittle hair	Coarse hair
Diarrhoea	Constipation

If a dysfunction is detected thyroid antibody levels should be determined to either microsomal (anti-TPO) or thyroglobulin (anti-TG). The first is usually more sensitive and specific, but both can be detected in the general population, and so great care should be considered when evaluating positive results without clear clinical findings. Anti-TSH receptor antibodies (TRAb) can be detected in Graves' disease, with or without simultaneous positivity for anti-TPO or anti-TG antibodies. A radioactive iodine uptake test (RAIU) is a very informative assay, even if not readily available to the general practitioner.

Hashimoto's disease most frequently presents with a low fT4, increased TSH, presence of thyroid autoantibodies and a decreased RAIU. But whilst autoantibodies are a hallmark, all the other signs can be of variable presence; the subclinical thyroiditis syndrome being specifically one condition where antibodies can be present with no other clinical findings. In doubtful situations biopsy can be an ultimate approach.

Graves' disease findings typically include thyrotoxicosis, goitre and exophthalmos, with raised fT4, suppressed TSH, positive TRAB detection and an elevated RAIU. Probable Graves' disease should be considered when at least one of these clinical findings is present with at least the first three laboratory conditions, and it should be suspected when at least one clinical finding is associated with raised fT4 and suppressed TSH. It should be emphasised that no positive TRAB test is necessary for a strong diagnostic probability.

In older patients it should be remembered that clinical symptoms and signs, including goitre, may be difficult to assess. For that reason TSH routine evaluation has been suggested as a cost-effective health screening strategy to be implemented every 5 years starting at age 35 on the average population, or more frequently in individuals at higher risk of developing thyroid dysfunction (personal or familial history of autoimmune thyroid disease, vitiligo, pernicious anaemia, diabetes mellitus or primary suprarenal insufficiency).

4 Diagnostic measurements for experts

The TSH assay is an internationally well standardized assay and so different manufacturers should provide comparable results, provided the sensitivity is of similar magnitude. The same applies reasonably to fT4 but significant variability can be expected between different manufacturers' results when the serum protein level is depleted as in severely ill patients. Total T3 is the most difficult assay to standardize and this is one of the reasons why it should be used with care when evaluating a dysfunctional thyroid status.

Autoantibodies assays were, up to some years ago, highly unreliable and results from different manufacturers were incomparable, both in interpretation and in quantification. Whilst recent standardization procedures have significantly removed the poor performance issue relating to positive/negative interpretation,

physicians should bear in mind that the current knowledge about the performance of older determinations can limit their use in the AITD diagnosis as well as in follow-up. There are no available universal standards for these autoantibodies and so different manufacturers can still produce quantifications which cannot be legitimately compared.

Other parameters such as serum cholesterol, triglycerides and alkaline phosphatase are often either increased in hypothyroidism or decreased in the hyperfunctional thyroid status.

5 Requirements for family practitioners

AITD are one of the most prevalent autoimmune diseases, and they should be especially considered in the elder population, due to their frequent partial or atypical presentation.

Functional thyroid assays (TSH and fT4) are one of the most sensitive forms of screening, and serum TSH is the single most reliable test to diagnose AITD induced forms of hypo or hyperfunction, and has been suggested to be considered a standard procedure for the general population every 5 years after the age of 35. Autoantibody test results should be considered very carefully when no dysfunctional status is present.

Occasionally goitre can be clinically undetectable and an ultrasound evaluation may be indicated when a strong suspicion remains after a negative physical examination.

Patients usually consult their general practitioners with vague symptoms of fatigue and depression or anxiety and irritability. Referral to the endocrinologist of suspected patients should provide fast and efficient management.

6 Management

Treatment of these diseases is addressed at the dysfunctional status. Only very exceptionally should an immunological approach be considered. Treatment includes adrenergic beta-blockers, antithyroid drugs, radioiodine (radioactive iodine 131) and thyroidectomy for the thyrotoxic status. Since surgery in a hyperthyroid patient is dangerous, preoperative treatment with antithyroid drugs is usually mandatory. Antithyroid treatment must be given for between six months and two years. Even then, on cessation of the drugs, the hyperthyroid state may recur. Therapy with radioiodine is the most common treatment in the United States, whilst antithyroid drugs and/or thyroidectomy are used more often in Europe, Japan and the rest of the world. For patients with a large goitre, thyroidectomy is often preferred because of its high efficacy in restoring euthyroidism, although hypothyroidism can result when most of the thyroid is removed. Graves' ophthalmopathy

is treated with steroids, local radiation or surgery and anti-CD20 monoclonal antibodies have been used with some success.

Hypothyroidism must be treated with replacement thyroid hormones. Levothyroxine sodium is the treatment of choice for the management of hypothyroidism with extra care being recommended for those patients older than 50 years or in younger patients with a history of cardiac disease.

7 Follow up

Periodic monitoring is essential for the adequate management of hyper or hypo thyroid diseases. Since the treatment of these pathologies may last for several years, a follow-up protocol must be established in strict cooperation with the endocrinologist. Patient compliance with prescription must be adequately monitored and dosage adjustment due to drug interaction and changes in body weight or advancing age must be considered.

Initial evaluation should be repeated every 4 to 8 weeks until stabilization of the functional status is achieved. TSH normalization is the single most useful test to determine that the euthyroidism status has been achieved and that a decrease in patient visit frequency can be considered. It should be taken into account that serum TSH may remain suppressed in hyperthyroid treated diseases for a period of several months after fT4 normalization, so potentially inducing wrong interpretations. In these clinical conditions it is recommended that at least fT4 should also be monitored.

Treatment with anti-thyroid drugs, radioactive iodine and surgery usually require more extensive follow-up procedures that are not the scope of this short review.

If clinical (check weight at home) and laboratory euthyroid function persists patients can be re-evaluated yearly for 2 to 3 years and then at increasing intervals.

References

[1] Sgarbi J, Maciel R. Pathogenesis of autoimmune thyroid diseases. Arq Bras Endocrinol Metab 2009; 53: 234–4.

[2] Caturegli P, Kimura H, Rocchi R, Rose NR. Autoimmune thyroid diseases. Curr Opin Reumathol 2007; 19: 44–8.

[3] Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association Guidelines for the Detection of Thyroid Dysfunction. Arch Intern Med 2000; 160: 1573–5. [Erratum in: Arch Intern Med 2001; 161: 284.]

[4] Singer PA, Cooper DS, Levy EG, et al. Treatment Guidelines for Patients with Hyperthyroidism and Hypothyroidism. Standards of Care Committee, American Thyroid Association. JAMA 1995; 273: 808.