Autoimmune thyroid disease is the commonest category of autoimmune disease in humans. Prevalences of up to 10% are quoted, with a higher prevalence in women than men. The two leading types are Hashimoto’s type autoimmune thyroiditis (AIT), including the atrophic form, which presents as primary myxedema, and autoimmune thyroiditis, which is also known as Graves’ disease (or Basedow’s disease in a number of European countries). Rarer forms of autoimmune thyroiditis are silent thyroiditis, the iatrogenic thyroiditides, and postpartum thyroiditis. De Quervain’s sub acute thyroiditis and Riedel’s goiter are additional types of thyroiditis which are of non-autoimmune etiology, and will therefore be excluded from this discussion.

Methods

A literature search of PubMed was conducted from 1980 to 2006, using the following terms: Hashimoto’s thyroiditis, autoimmune thyroiditis, Graves’ disease, etiology, pathogenesis, anti-TPO auto antibodies, anti-Tg auto antibodies, TSH receptor auto antibodies, outcome prediction, endocrine ophthalmopathy.

Autoimmune thyroiditides

Classification

The commonest form of autoimmune thyroiditis (AIT) is hypertrophic thyroiditis of the Hashimoto type. As part of the process of lymphocytic destruction, this can develop into a secondary atrophic form. Silent thyroiditis is a clinically milder variant. In clinical practice this is often subsumed under the heading of AIT, and in any case, a definite categorization is only possible during the course of the illness. In postpartum thyroiditis, and in the iatrogenic thyroiditides, autoimmune elements can often be demonstrated, which is why this form is counted among the autoimmune thyroiditides.

Genetic and environmental factors

Studies have shown an association between HLA class 2 molecules DR3, DR4 and DR5 and the incidence of Hashimoto’s thyroiditis. However, the data are as yet inconclusive. The cytotoxic T cell surface molecule clearly has a role in AIT. Predisposing environmental
factors have also been described, including smoking and high iodine intake, both of which are associated with an increased incidence of AIT (1).

**Etiology and pathogenesis**

A recently published study using a transgenic mouse model suggested that a particular epitope of thyroperoxidase is recognized by cytotoxic T lymphocytes (2). All mice developed a lymphocytic infiltration similar to that seen in patients, a fall in serum T4 and T3 levels, and a rise in TSH (2). This suggests that parts of the thyroperoxidase molecule are the key locus of the immune process. Close analysis of the lymphocytic infiltrates of affected patients shows a Th1 cytokine profile, equating to a cytotoxic immune reaction (3). Cellular reactions against thyroglobulin (Tg), a further potential thyroid specific antigen, are currently...
viewed as secondary phenomena. The etiology of postpartum thyroiditis was unclear until recently. Recent studies point to an infiltration of the maternal thyroid by fetal cells (4). This leads to an immunological reaction with measurable thyroid specific antibodies. Iatrogenic thyroiditides are often seen following treatment with Th1 cytokines such as interferon alpha (IFN α) and Interleukin 2 (IL 2).

**Clinical picture**

The clinical picture can vary markedly between and within the various autoimmune thyroiditides. Symptoms and signs relate primarily to thyroid function, and can vary from a classical hyperthyroid picture, with tachycardia, weight loss and restlessness, to one of hypothyroidism, with tiredness, lassitude, bradycardia, constipation and cold intolerance. The initial hyperthyroid picture is explained by a lymphocytic destructive process with increased release of thyroid precursor hormone. Many patients with autoimmune thyroiditis, especially those with silent thyroiditis, are asymptomatic. In these patients the diagnosis is often made incidentally. The clinical course of postpartum thyroiditis is very variable and is masked by other factors such as the increased energetic demands placed upon the mother in the postpartum period. It can be characterized both by hyperthyroid and hypothyroid phases. In the longer term, a return to normal, physiological functioning is just as likely as persistent hypothyroidism.

**Imaging**

In addition to the history and physical examination, ultrasound is helpful in investigating AIT. The thyroid parenchyma is typically inhomogeneous and shows a diffuse pattern of reduced echogenicity, by contrast with healthy thyroid tissue, where the parenchyma is homogeneous and the echogenicity normal (figure). The thyroid is usually enlarged in Hashimoto's disease, but can be of normal size. Duplex sonography, however, shows increased vascularity. The atrophic form is characterized by a marked reduction in parenchymal volume (diagram 1). Thyroid scintigraphy is seldom necessary, and should only be used in exceptional circumstances such as in hyperthyroidism with uncertain antibody status.

**Biochemistry**

**Thyroid hormones**

Under physiological conditions, the central regulatory mechanism for thyroid function is the pituitary release of thyroid stimulating hormone (TSH). The serum TSH level is therefore an indirect marker of current thyroid hormone release, and hence of its delivery to end organs. In many cases basal TSA assay alone is therefore a satisfactory investigation for thyroid function. Where serum thyroid hormone levels are required, free hormone levels should be measured, as these represent a true reflection of peripherally available hormone. Total thyroxin assay without reference to protein binding (over 99% of thyroxin is protein bound) is unhelpful. Triiodothyronine (T3) can be assayed as total T3, because of the much-reduced protein binding of free T3. A single reading of increased T4 in the context of AIT suggests destructive hyperthyroidism.

**Antibody assay**

The immunological process triggered by thyroperoxidase is reflected in the patient's antibody status. It is known that the prevalence of TPO and thyroglobulin antibodies increases with increasing age, and that the prevalence of TPO antibodies is higher in all age groups than that of Tg antibodies (5). The Whickham survey, which studied 2 779 individuals over 20 years showed that women are significantly more likely to produce thyroid antibodies than men (6). At the end of the observation period thyroid specific antibodies were found in 26.4 % of women (median age 59 years) and 8.8 % of men (median age 58). It is notable that in 2% of women and 0.5 % of men, thyroid antibodies detected initially were later no longer detectable.

A cross sectional study of more than 17 000 US citizens from 1988 to 1994 (NHANES III) showed that 13% had TPO antibodies and 11.5% Tg antibodies (7). Of the Tg antibody positive individuals, 69.9 % were also positive for anti-TPO. Whereas of the TPO antibody positive individuals, only 54.5 % had Tg antibodies. An increased TSH level (> 4.5 mU/l) and
clinical hypothyroidism were highly significantly associated with TPO antibodies, but not with Tg antibodies. No anti-Tg antibodies were found in anti-TPO negative individuals with hypothyroidism. A metaanalysis carried out by the American Medical Association came to similar conclusions (8). No clear statement about the correlation between antibody titer and the risk of (subclinical) hypothyroidism is possible on the basis of current data.

Silent thyroiditis is often associated with a low or only transiently detectable anti TPO titer. Around 50% of pregnant women with TPO antibodies develop postpartum thyroiditis, of whom only 90% have anti TPO antibodies at the time of presentation. The relapse rate for postpartum thyroiditis is around 70% in antibody positive women.

In cytokine-induced thyroiditides, the probability of clinical hypothyroidism in IFN \(\alpha\) treatment is 3% to 4%. More than 5% of patients treated in this way develop anti-TPO antibodies. Some patients also show signs of hyperthyroidism, in the early stages. Similar results have been found in IL 2 treatment.

Antibodies against sodium iodide symporter play a secondary role in all AIT patients. Commercial assays for these antibodies are currently unavailable.

**Autoimmune hyperthyroidism**

In addition to autoimmune hyperthyroidism, Graves’ disease is associated with ocular involvement. However, the two terms are often used synonymously in practice. The incidence of Graves’ disease is about 40 cases per 100,000 population per year.

**Genetic and environmental factors.**

Early evidence of genetic associations with Graves’ disease came from studies in identical twins, which showed a concordance for Graves’ disease of around 20%. Positive associations have been described for the HLA molecules DR 3 and DQA1*0501. HLA DRB*0701 appears to be protective. However, the published data on these associations differ. An association with the CTLA-4 polymorphism has been described for both Hashimoto’s and Graves’ thyroiditides. Smokers have an increased, dose dependent risk of Graves’ disease (10).

**Etiology and pathogenesis**

Anti TSH receptor antibodies (TRAB), which, like TSH, bind the receptor and have a stimulatory effect with resulting hyperthyroidism, are pathognomonic for autoimmune thyroiditis. Hence, the TSH receptor (TSHR) is the principal antigen in hyperthyroidism. The cause of the development of these antibodies remains unclear. The receptor consists of a large N terminal extra cellular domain, which is responsible for the specificity of hormone recognition and binding, and seven transmembrane regions, across which the signal is transferred to the G protein. Most studies point to epitope regions in the N terminal extra cellular domain of the TSH receptor as the target for the autoimmune process (11–13).

**Clinical presentation**

Karl von Basedow first described the classic symptoms of autoimmune hyperthyroidism – tachycardia, exophthalmos and goiter – known as the "Merseburg triad" – in 1840. Because of the TSH receptor stimulation hyperthyroidism is almost always present. 50% of cases also show eye signs, including exophthalmos, retro bulbar pressure sensation, double vision, and increased tear production. These effects may in part be attributable to antibody binding to TSH receptors in the retro bulbar tissue (14). Pretibial myxedema and acropachy (clubbing and subperiostial new bone formation in the hands and feet) are extremely rare, occurring in only around 1% of cases.

**Imaging**

Ultrasound is, again, a key investigation in autoimmune hyperthyroidism. The thyroid gland is typically enlarged, mainly due to an increase in depth, with an inhomogeneous, diffuse, echo-poor parenchyma, which can sometimes appear in a fielded pattern. Duplex sonography often shows increased blood flow, which can be palpated, known as “thyroid storm” (diagram 1). Thyroid scintigraphy often shows an increased uptake of technetium. This investigation is generally unnecessary in diagnosing autoimmune hyperthyroidism, but can be useful where thyroid nodules are also present.
Biochemistry

Thyroid hormones: to determine the extent of hyperthyroidism it is necessary to ascertain the levels of basal TSH, free T4 and, where appropriate, free T3. Following initial down regulation and normalisation of the free hormone levels, treatment can be further refined on the basis of basal TSH alone.

The use of TSH receptor antibody assay to clarify the diagnosis: two basic methods exist for determining thyroid receptor antibody (TRAB) levels. The old test system is based on the competitive binding of the antibody in question with radioactively labelled bovine TSH (TBII assay) in a homogenised pig thyroid cell membrane. Results are quoted in U/l and have a normal range of up to 10 U/l with a grey area up to 15 U/l. The cloning of human TSH receptors has facilitated the establishment of a new TRAB test (15, 16). Various groups (17, 18) including our own have demonstrated markedly higher sensitivities without loss of specificity, compared with the older test. A further advantage of this assay is its comparability with the WHO standard, as it is measured in IU/l, rather than U/l. The diagnostic threshold value is in the region of 1.5 IU/l with a grey area between 1 and 1.5 IU/l (19). This assay allows a diagnosis of Graves’ disease to be made with a very high positive predictive value. This test is significantly more sensitive but also more expensive.

The use of TRAB assay in determining prognosis: a TRAB test based on the new assay is also useful in determining prognosis. This was only possible to a limited extent with the first generation assay. In one of their own studies, the authors showed that the relapse rate...
increases with increasing TRAB titers, and that the TRAB levels at six months after disease onset are important predictors of prognosis. A TRAB level of > 10 IU/l is associated with an extremely low probability of remission (diagram 2) (20). This was true for only a third of patients studied, in whom a positive predictive value of 96.4% was measured. Below this level no reliable prognostic conclusions could be drawn. The Essen group were able to confirm these findings in patients with 12 months’ illness (21). On the basis of these results, it may in future be possible to make decisions about the need for definitive treatment (radio iodine or surgery) just six months into the course of the illness. At present these decisions are not made until around 18 months.

The use of TRAB in predicting endocrine orbitopathy: the new TRAB assay allows the clinician to predict the course of endocrine orbitopathy (EO). As with the prediction of prognosis in thyroid function, TRAB titers relate to the progression of EO. Hence TRAB measurement is also useful from an ophthalmologic viewpoint (22).

Stimulating TRABs and blocking TRABs: in addition to quantitative measurement using commercially available assays, there is also the possibility of bioassay (23). This allows stimulating and blocking TRABs to be distinguished from one another. In bioassay, the cAMP content is measured in the culture medium of host cells transfected with TSH receptors following cultivation with the relevant sera. The authors have shown for stimulating TRABs that a stimulation index of 10 allows patients with persistent disease to be distinguished from those in remission. These results were also valid for antibody measurements six months into the disease process (24). Where the primary diagnosis was made later, this distinction was not possible (25). The difference between these two studies is most likely to relate to continually falling TRAB levels throughout the course of the disease. No differences exist between the two groups of patients for blocking TRAB antibodies. Because of the high laboratory costs, these investigations are confined to research settings, at present.

Further antibodies in Graves’ disease: 60 to 80% of patients with Graves’ disease also have Po antibodies. This is essentially a secondary phenomenon arising in increased antigen presentation on the thyroid cells, is of no therapeutic significance, and need not be pursued as part of the diagnostic work up of Graves’ disease. The same is true for Tg antibodies.
Conflict of Interest Statement
The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

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REFERENCES


8. Surks MI, Ortiz E, Daniels GH et al.: Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004; 291: 228–38.


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